International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL 58 (QUALITY) - STABILITY: CLIMATIC ZONES III AND IV
June 2018
For consultation at Step 4

Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

Recommended for Consultation at Step 4 of the VICH Process
in June 2018
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

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Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

1. INTRODUCTION

1.1 Objectives of the Guideline

This document is an annex to the VICH parent stability guideline, Stability Testing of New Veterinary Drug Substances and Medicinal Products (VICH GL3(R)) and provides guidance regarding the stability data package for a new veterinary drug substance and medicinal product to be included in a registration application submitted within the regions in climatic zones III and IV[1].

The guideline seeks to exemplify the core stability data package for new veterinary drug substances and medicinal 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 may be used when there are scientifically justifiable reasons.

1.2 Background

The world can be divided into four climatic zones, I-IV, based on the prevailing annual climatic conditions and the guideline published by the World Health Organization (see Appendix section).

The parent guideline (VICH GL3(R)) describes the stability data package for the three VICH regions, the European Union (EU), Japan, and the United States (US), which are all in Climatic Zones I and II. To harmonize with the long-term storage condition for Zone IVA, the intermediate storage condition in the General Case for Zones I and II in the parent guideline has been revised to 30°C ± 2°C/65% RH ± 5% RH. This condition of 30°C ± 2°C/65% RH ± 5% RH can also be a suitable alternative to 25°C ± 2°C/60% RH ± 5% RH as the long-term storage condition for Zones I and II. Therefore, the parent guideline can be followed to generate stability data package for a registration application in countries or regions in Climatic Zones I, II and IVA.

This guideline provides additional guidance on the storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IVB (hot and very humid) which are not covered by VICH GL3(R). For completeness, the conditions outlined in the parent guideline for Zones IVA (30°C ± 2°C/65% RH ± 5% RH or intermediate storage conditions), are listed again here in this guideline.

1.3 Scope of the Guideline

This guideline addresses the information to be submitted in registration applications for new veterinary drug substances and associated medicinal products.

This guideline does not seek to cover information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

Further guidance on stability testing of new dosage forms, medicated premixes, and on biotechnological/biological products can be found in VICH guidelines GL4, GL8, and GL17, respectively. Stability testing following first use of the product (e.g., first broaching of a vial) is not covered within this guideline.

2. GUIDELINES

2.1 Continuity with the Parent Guideline

This guideline should be used in conjunction with the parent guideline (VICH GL3(R)) and subsequently published quality guidelines and/or annexes (GL4, GL5, GL8, GL17 and GL45). The recommendations in the parent guideline and the associated guidelines as referenced, should be followed unless specific alternatives are described within this guideline. The following sections of the parent guideline can be considered common to any territory in the world and are not reproduced here:

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage conditions for drug substance or medicinal product in a refrigerator
- Storage conditions for drug substance or medicinal product in a freezer
- Stability commitment
- Evaluation
- Statements/labeling

2.2 Storage Conditions

2.2.1 General Case

For the "General Case" (as described in the parent guideline) for the drug substance and the medicinal product, the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

Study	**Climatic Zones**	**Storage condition**	**Minimum time period covered by data at submission**
Long Term	Zone III (Hot and Dry)	30°C ± 2°C/35% RH ± 5% RH	Drug substance: 12 months Medicinal product: 6 months
Long Term	Zone IVA (Hot and Humid)*	30°C ± 2°C/65% RH ± 5% RH	Drug substance: 12 months Medicinal product: 6 months

Long Term	Zone IVB (Hot and very Humid)	30°C ± 2°C/75% RH ± 5% RH	Drug substance: 12 months Medicinal Product: 6 months
Accelerated	Zone III	40°C ± 2°C/not more than (NMT) 25% RH	6 months
Accelerated	Zones IVA and IVB	40°C ± 2°C/75% RH ± 5% RH	6 months

* Same conditions as for the alternative long term storage conditions for Zones I and II as described in the parent guideline

No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV.

If the product is intended to be marketed in several climatic zones, it is up to the applicant to decide whether long term studies are performed at the highest temperature and humidity conditions, as applicable. Selection of the conditions for stability testing is based on a risk analysis.

2.2.2. Medicinal products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for medicinal 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 may be conducted under any controlled or ambient humidity condition.

2.2.3 Medicinal products packaged in semi-permeable containers

For aqueous-based drug products packaged in semi-permeable containers (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

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

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 a higher relative humidity and deriving the water loss at the lower relative humidity through calculation. This approach for deriving the water loss rate at the reference relative humidity can be followed as described in the parent guideline.

If the medicinal product is an aqueous-based product packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

2.2.4 Tests at elevated temperature and/or extremes of humidity

Special transportation and climatic conditions outside the storage conditions recommended in this guideline should be justified based on the results from studies in accelerated conditions (i.e. short excursions out of the long-term conditions), and if necessary be supported by additional data under more stressful conditions. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions. It is recommended that permeable containers should not be used for long term storage of products intended to be marketed in territories with extremely high humidity conditions such as in climatic Zone IVB, unless stability data is available to support such storage conditions.

Stability testing at a high humidity condition, e.g., 40°C/80% RH, is recommended for solid dosage forms in water-vapour permeable packaging, e.g., tablets in PVC/aluminum blisters, intended to be marketed in territories with extremely high humidity conditions such as in climatic Zone IVB. However, for solid dosage forms in primary containers designed to provide a barrier to water vapour, e.g. aluminum/aluminum blisters, stability testing at a storage condition of extremely high humidity is not considered necessary.

2.3 Additional Considerations

If it cannot be demonstrated that the drug substance or drug product will remain within its acceptance criteria when stored at the conditions as listed in section 2.2.1 for the duration of the proposed retest period or shelf life, the following options should be considered: (1) a reduced retest period or shelf life, (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

3. REFERENCES

1. WHO Technical Report Series, No.953, 2009, Annex 2; Stability Testing of active pharmaceutical ingredients and finished pharmaceutical products
2. VICH GL3(R):Stability Testing of New Veterinary Drug Substances and Medicinal Products
3. VICH GL4: Stability Testing of New Veterinary Dosage Forms
4. VICH GL5: Photostability Testing of New Veterinary Drug Substances and Medicinal Products
5. VICH GL8: Stability Testing for Medicated Premixes
6. VICH GL17: Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products
7. VICH GL45: Bracketing and Matrixing Designs For Stability Testing of New Veterinary Drug Substances and Medicinal Products

Appendix

The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. At the fortieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held in Geneva in October 2005, it was recommended to split the current Climatic Zone IV (hot and humid) into two zones: Climatic Zone IVA – for which 30 °C/65% RH will remain the standard long-term testing condition – and Climatic Zone IVB for which, if justified, 30 °C/75% RH will become the long-term testing condition.

Based on the latest survey conducted in 2010, the current WHO definition of climatic zones coupled with long term storage conditions are listed in the table below:

Climatic zone	**Definition**	**Criteria** Mean annual temperature measured in the open air air/mean annual partial water vapour pressure	**Storage condition**
I	Temperate climate	≤15°C/<11 hPa	21°C/45% RH
II	Subtropical and Mediterranean climates	>15 to 22°C/>11 to 18 hPa	25°C/60% RH
III	Hot, dry climate	> 22°C /≤15 hPa	30°C/35% RH
IVA	Hot, 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