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

#259

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

VICH GL58

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments on the guidance at https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2018-X-XXXX.

For further information regarding this document, contact Mai Huynh, Center for Veterinary Medicine (HFV-140), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-402-0669, email: Mai.Huynh@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either https://www.fda.gov/AnimalVeterinary/default.htm or https://www.regulations.gov/.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
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VICH GL 58 (QUALITY) - STABILITY:
CLIMATIC ZONES III AND IV
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This Draft Guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process.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 USA.

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Contains Nonbinding Recommendations
Draft – Not for Implementation

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

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

1. INTRODUCTION

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

1.1 Objectives of the Guidance

This document is an annex to the VICH parent stability guidance, CVM Guidance for Industry (GFI) #73/VICH GL3(R), "Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)"[1] and provides guidance regarding the stability data package for a new veterinary drug substance and medicinal product to be included in a registration or application submitted within the regions in climatic zones III and IV.

The guidance seeks to exemplify the core stability data package for new veterinary drug substances and medicinal products, but leaves 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 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 guidance, GFI #73/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 guidance 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

[1] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052387.pdf

the long-term storage condition for Zones I and II. Therefore, the parent guidance can be followed to generate the stability data package for a registration or application in countries or regions in Climatic Zones I, II and IVA.

This guidance 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 GFI #73/VICH GL3(R). For completeness, the conditions outlined in the parent guidance for Zones IVA (30°C ± 2°C/65% RH ± 5% RH or intermediate storage conditions), are listed again here in this guidance.

1.3 Scope of the Guidance

This guidance addresses the information to be submitted in registrations or applications for new veterinary drug substances and associated medicinal products. This guidance 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 GFI #74/VICH GL4, "Stability Testing of New Veterinary Dosage Forms,"[2] GFI #91/VICH GL8, "Stability Testing for Medicated Premixes,"[3] and GFI #99/VICH GL17, "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products,"[4] respectively. Stability testing following first use of the product (e.g., first broaching of a vial) is not covered within this guidance.

2. Guidances

2.1 Continuity with the Parent Guidance

This guidance should be used in conjunction with the parent guidance GFI #73/VICH GL3(R) and subsequently published quality guidances and/or annexes GFI #74/VICH GL4, GFI #75/VICH GL5, "Stability Testing-Photostability Testing of New Veterinary Drug Substances and Medicinal Products,"[5] GFI #91/VICH GL8, GFI #99/VICH GL17, and GFI #198/VICH GL45, "Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products."[6] The recommendations in the parent guidance and the associated guidances, as referenced, should be followed unless specific alternatives are described within this guidance. The following sections of the parent guidance 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

[2] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052389.pdf
[3] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052429.pdf
[4] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052438.pdf
[5] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052391.pdf
[6] https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM172839.pdf

- 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 guidance) 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 guidance.

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 should be 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 can 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 guidance), 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 guidance.

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 guidance 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 critical.

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. GFI #73/VICH GL3(R), "Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)"[7]
3. GFI #74/VICH GL4, "Stability Testing of New Veterinary Dosage Forms"
4. GFI #75/VICH GL5, "Stability Testing-Photostability Testing of New Veterinary Drug Substances and Medicinal Products"
5. GFI #91/VICH GL8, "Stability Testing for Medicated Premixes"
6. GFI #99/VICH GL17, "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products"
7. GFI #198/VICH GL45, "Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products"

[7]All FDA guidances mentioned in this document are also available at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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