



1 19 July 2018
2 EMA/CVMP/VICH/335918/2016
3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 **VICH GL58 Stability Testing of New Veterinary Drug**
5 **Substances and Medicinal Products in Climatic Zones III**
6 **and IV**
7 **Draft**

Draft agreed by VICH Steering Committee	June 2018
Adoption by CVMP for release for consultation	19 July 2018
Transmission to interested parties	30 July 2017
End of consultation (deadline for comments)	31 December 2018

8
9

Comments should be provided using this [template](#). The completed comments form should be sent to vet-guidelines@ema.europa.eu

10
11





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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72, Fax +32 2 543 75 85
e-mail: sec@vichsec.org – Website: www.vichsec.org

TABLE OF CONTENTS

1. INTRODUCTION.....3

1.1 Objectives of the guideline.....3

1.2 Background.....3

1.3 Scope of the guideline.3

2. GUIDELINES.....4

2.1 Continuity with the Parent Guideline.....4

2.2 Storage Conditions.....4

2.2.1 General Case.....4

2.2.2 Medicinal products packaged in impermeable containers.....5

2.2.3 Medicinal products packaged in semi-permeable
containers.....5

2.2.4 Tests at elevated temperature and/or extremes of humidity.....6

2.3 Additional Considerations..... 6

3. REFERENCES.....6

APPENDIX.....7

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 IV¹.

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 $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$. This condition of $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ can also be a suitable alternative to $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ 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 ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ 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.

48 Further guidance on stability testing of new dosage forms, medicated premixes, and on
 49 biotechnological/biological products can be found in VICH guidelines GL4, GL8, and GL17,
 50 respectively. Stability testing following first use of the product (e.g., first broaching of a
 51 vial) is not covered within this guideline.
 52

53 **2. GUIDELINES**

54 **2.1 Continuity with the Parent Guideline**

55
 56 This guideline should be used in conjunction with the parent guideline (VICH GL3(R)) and
 57 subsequently published quality guidelines and/or annexes (GL4, GL5, GL8, GL17 and GL45).
 58 The recommendations in the parent guideline and the associated guidelines as referenced,
 59 should be followed unless specific alternatives are described within this guideline. The
 60 following sections of the parent guideline can be considered common to any territory in the
 61 world and are not reproduced here:

- 62
 63
 - Stress testing
- 64
 - Selection of batches
- 65
 - Container closure system
- 66
 - Specification
- 67
 - Testing frequency
- 68
 - Storage conditions for drug substance or medicinal product in a refrigerator
- 69
 - Storage conditions for drug substance or medicinal product in a freezer
- 70
 - Stability commitment
- 71
 - Evaluation
- 72
 - Statements/labeling

73 **2.2 Storage Conditions**

74 **2.2.1 General Case**

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

78

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

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

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

83
84 If the product is intended to be marketed in several climatic zones, it is up to the applicant
85 to decide whether long term studies are performed at the highest temperature and humidity
86 conditions, as applicable. Selection of the conditions for stability testing is based on a risk
87 analysis.

88
89 **2.2.2. Medicinal products packaged in impermeable containers**

90
91 Sensitivity to moisture or potential for solvent loss is not a concern for medicinal products
92 packaged in impermeable containers that provide a permanent barrier to passage of
93 moisture or solvent. Thus, stability studies for products stored in impermeable containers
94 may be conducted under any controlled or ambient humidity condition.

95
96 **2.2.3 Medicinal products packaged in semi-permeable containers**

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

100

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

101
102 An alternative approach to studying at the low relative humidity as recommended in the
103 table above (for either long-term or accelerated testing) is performing the stability studies
104 under a higher relative humidity and deriving the water loss at the lower relative humidity
105 through calculation. This approach for deriving the water loss rate at the reference relative
106 humidity can be followed as described in the parent guideline.

107

108 If the medicinal product is an aqueous-based product packaged in a semi-permeable
109 container, appropriate information should be provided to assess the extent of water loss.
110

111 **2.2.4 Tests at elevated temperature and/or extremes of humidity**

112 Special transportation and climatic conditions outside the storage conditions recommended
113 in this guideline should be justified based on the results from studies in accelerated
114 conditions (i.e. short excursions out of the long-term conditions), and if necessary be
115 supported by additional data under more stressful conditions. For example, these data can
116 be obtained from studies on one batch of drug product conducted for up to 3 months at
117 50°C/ambient humidity to cover hot and dry conditions and at 25°C/80% RH to cover
118 extremely high humidity conditions. It is recommended that permeable containers should
119 not be used for long term storage of products intended to be marketed in territories with
120 extremely high humidity conditions such as in climatic Zone IVB, unless stability data is
121 available to support such storage conditions.

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

128 **2.3 Additional Considerations**

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

134

135 **3. REFERENCES**

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

148

149

150 **Appendix**

151
 152 The mean kinetic temperature in any part of the world can be derived from climatic data,
 153 and the world can be divided into four climatic zones, I-IV. At the fortieth meeting of the
 154 WHO Expert Committee on Specifications for Pharmaceutical Preparations held in Geneva in
 155 October 2005, it was recommended to split the current Climatic Zone IV (hot and humid)
 156 into two zones: Climatic Zone IVA – for which 30 °C/65% RH will remain the standard long-
 157 term testing condition – and Climatic Zone IVB for which, if justified, 30 °C/75% RH will
 158 become the long-term testing condition.

159
 160 Based on the latest survey conducted in 2010, the current WHO definition of climatic zones
 161 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

162