INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III AND IV

Q1F

Current *Step 4* version
dated 6 February 2003

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q1F
Document History

First Codification	History	Date	New Codification **November 2005**
Q1F	Approval by the Steering Committee under *Step 2* and release for public consultation.	7 February 2002	Q1F

Current *Step 4* version

Q1F	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	6 February 2003	Q1F

STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III AND IV

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 6 February 2003, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III AND IV

1. INTRODUCTION

1.1 Objectives of the Guideline

This guideline describes an approach to broader use of the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) and outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in Climatic Zones III and IV[1, 2].

1.2 Background

The parent guideline describes the stability data package for the ICH tripartite regions (EC, Japan, and the United States), which are in Climatic Zones I and II. The parent guideline can be followed to generate stability data packages for registration applications in other countries or regions in Zones I and II. For territories in Climatic Zones III and IV, the data package as described in the parent guideline can be considered applicable except for certain storage conditions. An approach for classification of countries according to Climatic Zones I, II, III, and IV can be found in the literature[3,4].

The World Health Organization (WHO) has published a guideline "Stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms" (WHO Technical Report Series, No 863, Annex 5), updated in the Report of the thirty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, 22-26 October 2001. The WHO guideline describes stability testing recommendations, including storage conditions for all four climatic zones.

The stability testing recommendations in this guideline are based on the parent guideline and the WHO guideline. To harmonise with the long-term storage condition for Zones III and IV, the intermediate storage condition in the General Case for Zones I and II in the parent guideline is changed 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.

1.3 Scope of the Guideline

This document is an annex to the parent guideline and recommends the long-term storage condition for stability testing of a new drug substance or drug product for a registration application in territories in Climatic Zones III and IV.

2. GUIDELINES

2.1 Continuity with the Parent Guideline

This guideline should be used in conjunction with the parent guideline and subsequently published annexes (Q1B, Q1C, Q1D, Q1E, Q5C). The recommendations in the parent guideline and annexes 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 product in a refrigerator
- Storage conditions for drug substance or product in a freezer
- Stability commitment
- Evaluation
- Statements/labelling

2.2 Storage Conditions

2.2.1 General Case

For the "General case" (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/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV. Therefore, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in Q1E are applied.

2.2.2 Aqueous-based drug 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	12 months
Accelerated	40°C ± 2°C/not more than 25 % RH ± 5% RH	6 months

As described in the parent guideline, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio (see table below for examples).
The ratio of water loss rates at a given temperature is calculated by the general formula (100 – reference % RH)/(100 – alternative % RH).

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

2.2.3 Tests at elevated temperature and/or extremes of humidity

Special transportation and climatic conditions outside the storage conditions recommended in this guideline should be supported by additional data. 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 extremely hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions[2].

Stability testing at a high humidity condition, e.g., 25°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 in Zone IV. 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 30°C ± 2°C/65 % RH ± 5 % RH 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. Schumacher, P.
"Aktuelle Fragen zur Haltbarkeit von Arzneimitteln [Current questions on drug stability]"
Pharmazeutische Zeitung, 119: 321-324, 1974

2. Grimm, W.
"Storage Conditions for Stability Testing – Long term testing and stress tests"
Drugs made in Germany, 28: 196-202, 1985 (Part I) and 29: 39-47, 1986 (Part II)

3. Dietz, R., Feilner, K., Gerst, F., Grimm, W.
"Drug Stability Testing – Classification of countries according to climatic zone"
Drugs made in Germany, 36: 99-103, 1993

4. Grimm, W.
"Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV"
Drug Development and Industrial Pharmacy, 24, 313-325, 1998