

## **1.6**

### **ICH Q1F Guideline**

#### **Stability Data Package for Registration in Climatic Zones III and IV**

#### **Step 4 in the ICH process**

#### **Comments for its application**

## 1. General Consideration

### Definition and storage conditions for the four climatic zones

| Climatic zone | Definition                                | Storage condition |
|---------------|---|-------------------|
| I             | temperate climate                         | 21°C/45% r.h.     |
| II            | subtropical and<br>Mediterranean climates | 25°C/60% r.h.     |
| III           | hot, dry climate                          | 30°C/35% r.h.     |
| IV            | hot, humid climate                        | 30°C/70% r.h.     |

## 1. General Consideration

### Criteria used to classify a site according to climatic zone

| Criteria   | Guidevalues for individual climatic zone |                |               |           |
|--|--|----------------|---------------|-----------|
|  | I  | II             | III           | IV        |
| Mean annual temperature measured in the open air | up to 15°C                               | > 15 – 22°C    | > 22°C        | > 22°C    |
| Calculated mean annual Temperature (< 19°C)      | up to 20.5°C                             | > 20.5 – 24°C  | > 24          | > 24      |
| Mean annual water Vapour partial pressure        | up to 11 mbar                            | > 11 – 18 mbar | up to 15 mbar | > 15 mbar |

#### Countries assigned to the climatic zones III and IV (4):

- America:** Barbados, Belize, Brazil, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Columbia, Cuba, Nicaragua, Dutch Antilles, Panama, Paraguay, Puerto Rico, Venezuela. All these countries are assigned to CZ IV.
- Africa:** Angola, Ethiopia, Benin, Botswana (111), Burkino Faso, Burundi, Djibouti, Ivory Coast, Gabon, Gambia, Ghana, Guinea, Cameroon, Kenya, Longo, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Chad (111), Uganda, Zaire, Central African Republic
- Asia:** Bahrain, Bangladesh, Hong Kong, India, Indonesia, Iraq (111), Jordan (111), Kampuchea, Qatar, Kuwait, Laos, Malaysia, Maldives Islands, Myanmar, Oman, Pakistan, Philippines, Saudi Arabia, Singapore, Sri Lanka, Taiwan, Thailand, United Arab Emirates, Vietnam, Yemen
- Australian/  
Oceanic:** Fiji, Society Islands, Marshall Islands, New Caledonia, Papua - New Guinea, Samoan, Tonga

#### Storage conditions for countries of III and IV

The climatic conditions in a series of cities of the climatic zones III and IV have been, investigated. Thereby measured data (in the open) and calculated data were contrasted (5).

For these countries the storage conditions have to be derived.

### Cities of climatic zone III

| City      | measured data   |                              | calculated data          |                        |                              | days per annum with temp. above 30°C | days per annum with temp. above 40°C |
|-----------|-----------------|------------------------------|--------------------------|------------------------|------------------------------|--------------------------------------|--------------------------------------|
|           | temp.<br>[ °C ] | partial pressure<br>[ mbar ] | temp 19°C used<br>[ °C ] | rel. humidity<br>[ % ] | mean kinetic temp.<br>[ °C ] |                                      |                                      |
| Aswan     | 27.0            | 10.0                         | 28.3                     | 26.0                   | 30.0                         | 20                                   | 20                                   |
| Baghdad   | 22.7            | 11.0                         | 25.7                     | 33.3                   | 27.0                         | 15                                   | 15                                   |
| Elat      | 25.0            | 12.0                         | 26.4                     | 34.9                   | 28.3                         | 30                                   | 5                                    |
| Khartoum  | 29.5            | 11.8                         | 29.9                     | 28.0                   | 32.5                         | 40                                   | 15                                   |
| Mossul    | 20.2            | 12.0                         | 24.5                     | 39.0                   | 25.7                         | 20                                   | 10                                   |
| New Delhi | 24.8            | 14.5                         | 26.8                     | 41.2                   | 27.9                         | 30                                   | 5                                    |
| Riyadh    | 24.9            | 8.0                          | 26.7                     | 22.8                   | 28.0                         | 15                                   | 20                                   |
| Suez      | 22.5            | 13.5                         | 24.4                     | 44.2                   | 25.4                         | 15                                   | 0                                    |
| Jerusalem | 22.8            | 14.5                         | 24.6                     | 46.9                   | 25.8                         | 30                                   | 0                                    |
| mean      | 24.4            | 11.9                         | 26.4                     | 35.1                   | 27.8                         | 24                                   | 10                                   |

### Cities of climatic zone IV

| City      | measured data  |                                 | calculated data                |                         |                                   | derived data           |                                       |
|-----------|----------------|---------------------------------|--------------------------------|-------------------------|-----------------------------------|------------------------|---------------------------------------|
|           | Temp.<br>[°C ] | partial<br>pressure<br>[ mbar ] | temp.<br>19°C<br>used<br>[°C ] | re.<br>humidity<br>[% ] | mean<br>kinetic<br>temp.<br>[°C ] | Temp.<br>30°C<br>[°C ] | calculated<br>re.<br>humidity<br>[% ] |
| Bangkok   | 28.1           | 28.6                            | 28.1                           | 75.2                    | 29.1                              | 30                     | 67.4                                  |
| Belem     | 26.2           | 32.2                            | 26.2                           | 92.5                    | 27.6                              | 30                     | 75.9                                  |
| Bombay    | 26.9           | 27.0                            | 26.9                           | 76.2                    | 27.6                              | 30                     | 63.6                                  |
| Calcutta  | 26.3           | 25.5                            | 26.3                           | 74.5                    | 27.0                              | 30                     | 60.1                                  |
| Darwin    | 28.1           | 24.0                            | 28.1                           | 63.1                    | 29.1                              | 30                     | 56.6                                  |
| Jakarta   | 26.8           | 27.9                            | 26.8                           | 79.2                    | 27.4                              | 30                     | 65.8                                  |
| Karachi   | 25.5           | 23.5                            | 26.0                           | 69.9                    | 26.4                              | 30                     | 55.5                                  |
| Manila    | 27.2           | 28.0                            | 27.2                           | 77.6                    | 28.2                              | 30                     | 66.0                                  |
| Madras    | 28.6           | 29.0                            | 28.6                           | 74.1                    | 29.7                              | 30                     | 68.3                                  |
| Maracaibu | 29.0           | 28.5                            | 29.0                           | 68.3                    | 31.0                              | 30                     | 67.2                                  |
| Recife    | 26.3           | 25.8                            | 26.3                           | 75.4                    | 26.7                              | 30                     | 60.8                                  |
| Singapore | 27.3           | 28.3                            | 27.3                           | 77.7                    | 27.9                              | 30                     | 66.5                                  |
| mean      | 27.2           | 27.4                            | 27.2                           | 75.3                    | 28.1                              | 30                     | 64.5                                  |

The following information has to be given concerning the two tables

**Measured data:**

These data were measured in the open and represent the mean for a year.

**Calculated data:**

Drug products are stored in warehouses which may be tempered during the cold season. Therefore 19°C is set in for all temperatures below 19°C. For the corresponding calculated mean temperature the relative humidity is determined.

## Storage conditions for countries of III and IV

### Mean kinetic temperature:

If a mean temperature is calculated and the difference between two temperatures is  $> 5^{\circ}\text{C}$  the mean kinetic temperature should be calculated instead of the arithmetic mean temperature. This derives from the fact that the temperature dependency is not linear but logarithmic according to the Arrhenius equation. Haynes (7) has derived an equation based on the Arrhenius equation to calculate the  $T_{\text{mkt}}$ , the mean kinetic temperature:

$$T_{\text{mkt}} = \frac{\Delta E/R}{-\ln \frac{e^{-\Delta E/RT_1} + e^{-\Delta E/RT_2} + e^{-\Delta E/RT_n}}{n}}$$

$\Delta E$ : activation energy in  $\text{kJ} \cdot \text{mol}^{-1}$  for which  $83 \text{ kJ mol}^{-1}$  can be set in (5).

Example:

20°C, 40°C: arithmetic mean temperature: · 30°C  
 mean kinetic temperature: · 34.4°C

The calculated mean kinetic temperatures are 27.8°C and 28.1°C. 30°C was therefore fixed as the storage temperature for both, to include a margin of safety of 2.2 resp. 1.9°C.

The measured, calculated and derived data for climatic zones III and IV are summarized in the following tables 5 and 6.

### Measured, calculated and derived data

| Climatic zone | measured data |                          | calculated data           |                     | derived data |                     |
|---------------|---------------|--------------------------|---------------------------|---------------------|--------------|---------------------|
|               | Temp.         | Partial Pressure [ mbar] | Mean kinetic Temp. [ °C ] | rel. humidity [ % ] | Temp. [ °C ] | rel. humidity [ % ] |
| III           | 24.4          | 11.9                     | 27.8                      | 35.1                | 30           | 35                  |
| IV            | 27.2          | 27.4                     | 28.1                      | 75.3                | 30           | 70                  |

### Storage conditions and margin of safety

| Climatic zone | Calculated storage condition |          | Derived storage condition |       |          | Margin of safety |           |
|---------------|------------------------------|----------|---------------------------|-------|----------|------------------|-----------|
|               | [°C ]                        | [ mbar ] | [°C ]                     | [ % ] | [ mbar ] | [Δ°C ]           | [Δ mbar ] |
| II            | 21.7                         | 13.5     | 25                        | 60    | 19.0     | 3.3              | 5.5       |
| III           | 27.8                         | 11.9     | 30                        | 35    | 14.9     | 2.2              | 3.0       |
| IV            | 28.1                         | 27.4     | 30                        | 70    | 29.7     | 1.9              | 2.3       |
| IV*           | 28.0                         | 27.4     | 30                        | 65    | 27.6     | 2.0              | 0.2       |

\* the new storage condition for climatic zone IV

### Measured and calculated data in warehouses

| Climatic zone | Cities with warehouses  | measured data in warehouses |            | calculated data            |            |                   |            |
|---------------|---|-----------------------------|------------|----------------------------|------------|-------------------|------------|
|               |   | [ °C ]                      | [ % r.h. ] | for cities with warehouses |            | for climatic zone |            |
|               |   | [ °C ]                      | [ % r.h. ] | [ °C ]                     | [ % r.h. ] | [ °C ]            | [ % r.h. ] |
| III           | New Delhi, Khartoum   | 26                          | 53.5       | 28.4                       | 35         | 27.9              | 35.1       |
| IV            | Abidjan, Bangkok, Bombay, Colombo, Dacca, Madras, Rio de Janeiro, Signapore | 28.4                        | 30.0       | 26.4                       | 75.0       | 27.4              | 75.8       |

Conclusions:

- Measured data in warehouses are in line with calculated data for these cities
- Applied procedure to calculate data has been proved by the data in warehouses
- The derived storage conditions are well above the measured data in warehouses and the calculated mean data for climatic zones III and IV.

# ICH Q1F

## 1. Introduction

### 1.1 Objectives of the Guideline

- Application of ICH Q1A(R) in countries of Climatic zones III and IV

### 1.2 Background

- Long term storage condition is different from 25°C/60% r.h.
- Harmonization with WHO guideline for world wide marketing

### 1.3 Scope of the Guideline

- Annex to Q1A(R2) to market drug substances and drug products in Climatic Zone III and IV

## 2. Guidelines

### 2.1 Continuity with the Parent Guideline

- Parent guideline and published annexes should be followed
- Following sections are not reproduced
  - Stress testing
  - Selection of batches
  - Container closure system
  - Specifications
  - Testing frequency
  - Statements/labeling
  - Refrigerated storage
  - Freezer storage
  - Semi-permeable or impermeable containers

## 2. Guidelines

### 2.2 Storage Conditions

#### General Case

| Study       | Storage condition             | Minimum time period Covered by data at submission |
|-------------|-------------------------------|---|
| Long term   | 30°C ± 2°C/65% r.h. ± 5% r.h. | 12 months   |
| Accelerated | 40°C ± 2°C/75% r.h. ± 5% r.h. | 6 months  |

- For application in climatic zone II 30°C/65% r.h. can replace 25°C/60%
- Intermediate condition 30°C/60% r.h will be changed to 30°C/65% r.h



## 2.2.2 Aqueous based drug products packed in semi-permeable containers

| Study       | Storage conditions                           | Minimum time period covered by data at submission |
|-------------|--|---|
| Long-term   | 30°C ± 2°C/35% r.h. ± 5% r.h.                | 12 months   |
| Accelerated | 40°C ± 2°C/ not more than 25% r.h. ± 5% r.h. |   |

### Table for calculation if “normal storage conditions” are applied

| Alternative relative humidity | Reference relative humidity | Ratio of water loss rates at a given temperature |
|-------------------------------|-----------------------------|--|
| 65% r.h.                      | 35% r.h.                    | 1.9  |
| 75% r.h.                      | 25% r.h.                    | 3.0  |

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

Examples:

- 3 months 50°C and ambient humidity
- 25°C/ 80% r.h.

## 2.3 Additional Considerations

If drug product will not remain within acceptance criteria when stored at 30°C ± 2°C/65% r.h. ± 5% r.h. for proposed shelf life: reduced shelf-life or more protective container or statement in labelling

## 2.4 Cautionary Note on data Packages for Climatic Zones III and IV

- Container closure system for climatic zone II may not be suitable for climatic zones III and IV
- Cautionary statements in the labeling may be necessary

## Prediction of applicable container closure systems for climatic zones III and IV

| Dosage form | Climatic zone | Container closure system  |
|-------------|---------------|---|
| Solid       | III           | Generally no limitations  |
|             | IV            | Tight containers for hygroscopic drug products                                      |
| Semisolid   | III           | Tight containers are necessary  |
|             | IV            | Generally no limitations but permeable containers have to be checked carefully      |
| Liquid      | III           | Tight containers are necessary  |
|             | IV            | Generally no limitations but some permeable containers have to be checked carefully |