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# The Mean Kinetic Temperature and Relative Humidity for Drugs and Products Stability Testing in Taiwan

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## ABSTRACT

**In stability testing, the mean kinetic temperature (MKT) and relative humidity (RH) are two important factors which have an impact on the determination of the shelf-life of a drug product. This report presents the MKT and RH of Taiwan based on climate data from different areas of Taiwan between the years of 1991 and 1995. The data used in the calculation is from the Central Weather Bureau of Taiwan. Activation energies of 10 to 30 Kcal/mol are considered. The results show that the MKT of Taiwan is 24.5℃ given a typical activation energy of 20 Kcal/mol, and the RH is 77%. Drug products degrade faster under higher MKT and RH. Based on analogous safety margins for MKT and RH in climatic zones I (19.7℃/43.9%, MKT/RH) and II (22.8℃/52.9%) as specified in the international conference on harmonization (ICH) stability testing guideline, the long-term storage test conditions for Taiwan would be 28 ± 2℃ and 90 ± 5% for temperature and humidity, respectively. These derived storage conditions are in fact 3℃ and 17% higher than those in the ICH guideline specified for the tripartite countries (EC, Japan and USA). For a 3℃ increment in MKT, the degradation rate constant will actually increase by about 34%. In consequence, a product marketed in Taiwan will only have about 75% of the shelf-life that it would have in the tripartite countries. In this communication, the implications of the climatic conditions of Taiwan are examined. Appropriate storage test conditions for drugs and products stability testing in Taiwan are also proposed.**

*Key words:* **mean kinetic temperature, relative humidity, stability test, Taiwan.**

## INTRODUCTION

After ten years of study, the international conference on harmonization (ICH) of technical requirements for the registration of pharmaceuticals for human use endorsed the ICH harmonized tripartite guideline for stability testing of new drug substances and products[(1)]. The guideline specifies the stability testing requirement for a Registration Application within the three areas of

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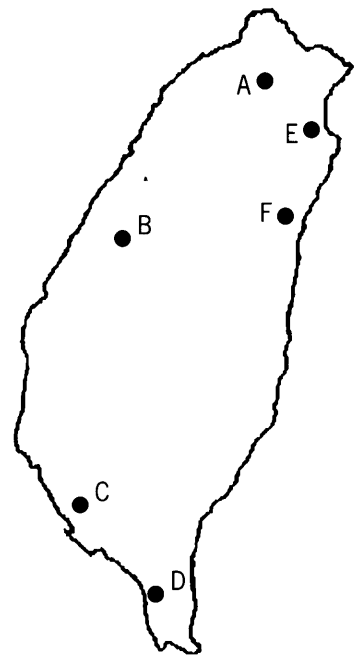
the EC (European Community), Japan and USA. Although it is primarily focused on new drug substances and products, the storage test conditions are also applied to generic drugs[2] and new dosage forms[3] in the USA. The suggested testing temperatures and relative humidities (RH) for the long-term, accelerated and intermediate storage tests are based on criteria proposed by Grimm in 1986[4]. The mean kinetic temperature (MKT)/RH that Grimm derived for climate zone I (EC) and zone II (USA and Japan) are 19.7℃/43.9% and 22.8℃/52.9%, respectively, with an addition of a suggested safety margin. The climate of the earth was in fact divided into four zones by Futscher and Schumacher[5], namely, zone I (temperate climate), zone II (Medite-rranean-like and subtropical climates), zone III (hot dry climate) and zone IV (hot humid tropical climate). The MKT and RH for each zone was calculated by Grimm[4] from selected cities in the corresponding zones. The climate of Taiwan is relatively humid and subtropical. It could not be classified into any of the four zones. It has higher temperatures and humidity than zone II. Although it is similar in humidity to zone IV, it has lower temperatures than the latter. Due to the fact that Taiwan has different climatic conditions from any of the four zones, modification of the ICH stability guideline is essential if it is to be implemented in Taiwan.

This communication presents the mean kinetic temperature and relative humidity of Taiwan calculated from data collected between 1991 and 1995. Appropriate storage test conditions for drugs and products stability testing in Taiwan are also proposed.

## MATERIALS AND METHODS

I. *Climate Data*

The monthly averaged climate data of six geographically representative cities in recent five




A: Taipei
B: Taichung
C: Kaohsiung
D: Hungchung
E: I-Lang
F: Hualein

**Figure 1.** Six geographically representative parts of Taiwan.

**Table 1.** Summary statistics of the climatic data in Taiwan[a] (mean ± SD)

| City | RH (%) | High/Low | Temp (℃) | High/Low |
|---|---|---|---|---|
| Taipei | 74.8 ± 1.2 | 85/65 | 22.8 ± 4.9 | 30.6/14.3 |
| I-lang | 82.9 ± 0.9 | 90/75 | 22.3 ± 4.4 | 29.0/14.7 |
| Taichung | 75.1 ± 0.8 | 82/70 | 23.3 ± 4.4 | 29.1/15.5 |
| Hualein | 76.4 ± 1.1 | 84/68 | 23.4 ± 3.7 | 28.9/16.7 |
| Kaohsiung | 74.1 ± 0.9 | 82/67 | 25.0 ± 3.6 | 29.7/18.4 |
| Hungchung | 75.9 ± 1.4 | 88/66 | 25.1 ± 2.8 | 28.8/20.1 |
| TAIWAN | 76.5 ± 5.0 | 90/65 | 23.6 ± 4.2 | 30.6/14.3 |

[a]: Based on five years of recent (1991-1995) climatic data provided by the Central Weather Bureau, Taiwan.

years (1991-1995) were obtained from the Central Weather Bureau, Taiwan. The location of each city is depicted in Figure 1 and the corresponding summary statistics listed in Table 1.

II. *Mean Kinetic Temperature (MKT)*

The formula derived by Haynes[6] as shown below was used to calculate the MKTs for the six cities and for the entire area of Taiwan.

$$MKT = \frac{\frac{-\Delta H}{R}}{\ln \frac{e^{\frac{-\Delta H}{RT_1}} + e^{\frac{-\Delta H}{RT_2}} + .... + e^{\frac{-\Delta H}{RTn}}}{n}}$$

Where MKT is the mean kinetic temperature in K (degrees Kelvin); $\triangle H$ is the activation energy in Kcal/mol for the degradation reaction; R is the gas constant in calmol-1K-1; Ti is the average temperature of the i-th month in K (degrees Kelvin).

III. *Relative Humidity*

The weather of Taiwan is actually hot and humid. In particular, the high humidity has been one of the most important issues in the storage of drug products in Taiwan. The highest monthly average of RH in five recent years was 90%, and in no city anywhere in Taiwan was the RH lower than 65%. In order to take into account the variation of humidity, a 99% confidence upper limit was calculated and used as the typical humidity.

## RESULTS AND DISCUSSION

I. *Mean Kinetic Temperature and Relative Humidity of Taiwan*

The MKTs and RHs of the six geographically

**Table 2.** Mean kinetic temperature (℃) and relative humidity (%) in Taiwan

| City | RH[a] (%) | Mean kinetic temperatures (℃) for various △H (Kcal/mol) | | | | |
|---|---|---|---|---|---|---|
| | | 10 | 15 | 20 | 25 | 30 |
| Taipei | 76 | 23.4 | 23.7 | 24.0 | 24.3 | 24.6 |
| I-lang | 84 | 22.8 | 23.0 | 23.3 | 23.5 | 23.8 |
| Taichung | 76 | 23.7 | 24.0 | 24.2 | 24.4 | 24.6 |
| Hualein | 77 | 23.8 | 23.9 | 24.1 | 24.3 | 24.5 |
| Kaohsiung | 75 | 25.3 | 25.5 | 25.7 | 25.8 | 25.9 |
| Hungchung | 77 | 25.3 | 25.4 | 25.5 | 25.6 | 25.7 |
| TAIWAN | 77 | 24.1 | 24.3 | 24.5 | 24.7 | 24.9 |

[a]: 99% confidence upper limit values.

**Table 3.** ICH stability testing conditions

| Area | MKT/RH | Tests | Safety margin |
|---|---|---|---|
| USA, EC, Japan | | Long-term (LT) | |
| | 21.3℃ | 25 ± 2℃ | MKT + 4℃ |
| | 48.4% | 60 ± 5% | RH + 12% |
| | | Accelerated | |
| | | 40 ± 2℃ | LT + 15℃ |
| | | 75 ± 5% | LT + 15% |
| | | Intermediate | |
| | | 30 ± 2℃ | LT + 5℃ |
| | | 60 ± 5% | LT + 0% |

**Table 4.** Stability test conditions of Taiwan equivalent to ICH guideline

| Area | MKT/RH | (MKT + safety margin)/(RH + safety margin) |
|---|---|---|
| Taiwan | 24.5℃<br>77% | Equivalent long-term storage condition<br>24.5 + 4 => 28 ± 2℃<br>77 + 12 => 90 + 5%<br>Equivalent accelerated test condition<br>28 + 15 => 43 ± 2℃<br>90 + 15 => 100%<br>Equivalent intermediate test condition<br>28 + 5 => 33 ± 2℃<br>90 + 0 => 90 ± 5% |

**Table 5.** Proposed stability testing conditions for Taiwan

| | |
|---|---|
| Long-term storage test | 28 ± 2℃/75 ± 5% |
| Accelerated test | 43 ± 2℃/90 ± 5% |
| Intermediate condition | 33 ± 2℃/75 ± 5% |

representative cities of Taiwan and their average are listed in Table 2. Since the activation energies of relevant room temperature degradation reactions usually fall in the range 12 to 24 Kcal/mol with a typical value of 19 to 20 Kcal/mol[7], the MKTs are calculated for the range of 10 to 30 Kcal/mol to ensure conservative margins. The MKTs are higher than the arithmetic mean temperature, and the larger the activation energy, the higher the MKT will be. This is because the temperature dependency and the level of activation energy of the drug degradation are taken into account by the Arrhenius equation[8]. The high temperature and activation energy should be given relatively large weight so that reasonable stability information can be obtained. For instance, a sample which is stored at 20℃ for one year and then 40℃ for a second year degrades much faster than would the same sample stored at the arithmetic mean of 30℃ for the entire two year period. The effect of temperature is also greater for reactions with a higher level of activation energy.

II. *Stability Test Conditions for Taiwan Area Based on ICH Guideline Principles*

Table 3 gives the stability testing conditions suggested by the ICH guideline and the safety margins used to define the storage test conditions. If the same magnitudes of safety margin are applied, the storage test conditions for Taiwan can be derived from the ICH guideline as shown in Table 4.

Tables 3 and 4 show that the derived storage test temperatures for the long-term, accelerated and intermediate condition tests in Taiwan are 3℃ higher than those of the ICH guideline. The influence of a 3℃ temperature increase in the drug degradation rate constant, k, can be elucidated as follows.

By differentiating the Arrhenius equation, the following equation can be derived.

$$\frac{dk}{k} = \frac{\Delta H}{RT}\left(\frac{dT}{T}\right)$$

Let temperature=25℃, dT=3° K, T=273.2+25° K and △H=20 Kcal/mol. One could then obtain

$$\frac{dk}{k} = \frac{20000 \times 3}{1.987 \times 298.2 \times 298.2} = 0.34$$

This implies that the degradation rate constant when the temperature is 28℃ would be 34% larger than the corresponding k at 25℃, given a typical activation energy of 20 Kcal/ mol[7]. Thus, the shelf-life of a drug product stored at 28℃ would be about 75% that of the same product stored at 25℃ because of the 3 degree increase in temperature. Consequently, a product of three years' shelf-life in the tripartite countries (EC, USA and Japan) may have only approximately 2.2 years

shelf-life in a store in Taiwan.

The humidity condition of 75 ± 5% for the accelerated stability testing in the ICH guideline would cover the average humidity conditions of the major populated areas of Taiwan (Taipei, Taichung and Kaohsiung). In addition, the effect of humidity on drug stability may be modified by the package used. Therefore, it is reasonable to adopt the ICH RH condition for the long-term and intermediate condition storage tests in Taiwan. However, since the accelerated stability test is intended to provide preliminary and supporting stability information for the product in its final packaged form under exaggerated storage conditions, a high humidity condition, such as 90 ± 5%, may then become appropriate. Table 5 shows the proposed stability test conditions of drug products in Taiwan.

The arguments and conclusions of this study may be used as a basis for drafting a new stability testing guideline for drugs and products in Taiwan.

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# 台灣地區藥品安定性試驗的平均動力學溫度及相對濕度

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## 摘 要

本報告根據1991至1995年的台灣氣象資料，導出台灣地區的平均動力學溫度及相對濕度。對10至30 Kcal / mol的活性化能位，計算各對應的平均動力學溫度。在台灣地區，分解反應的活性化能位爲20 Kcal / mol時，其平均動力學溫度爲24.5℃，代表性相對濕度爲77%。依據美國，日本及歐聯協調會（ICH）對氣候區Ⅰ及Ⅱ所用的安全係數，台灣地區藥品長期儲存試驗的溫濕度條件應爲28±2℃及90±5%。此條件比ICH所規定的條件高3℃及高17%。溫度昇高3℃會導致分解速率常數增大34%。因之，在ICH地區有三年有效期限的藥品，在台灣地區將只有二年的有效期限。本報告也提出適用台灣地區的藥品安定性試驗條件。

**關鍵詞**：平均動力學溫度，相對濕度，安定性試驗，台灣。