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Storage Conditions for Stability Testing of Pharmaceuticals in Hot and Humid Regions

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ABSTRACT A review of the methodology for determination of the storage conditions for stability testing according to Schumacher/Grimm is presented in this paper. The purpose is to provide scientific information useful for the definition of storage conditions for stability testing of pharmaceuticals suitable to the region where the product will be dispensed. Special attention is given to stability testing in the new markets located in developing countries with very hot and humid climates. Finally, storage conditions for stability testing in the Brazilian regions were derived and examined comparatively with the guidelines of the world health organization (WHO) and regulatory bodies. The storage conditions were derived from the calculated values of the mean kinetic temperature and the relative humidity (RH). These parameters were estimated from daily values of dry and dew point temperatures of all Brazilian capitals from 1998 to 2002; collected in the morning (9 a.m.), in the afternoon (3 p.m.), and at night (9 p.m.). The Brazilian Center of Weather Forecast and Climatic Studies of the National Institute of Spatial Research (CPTEC/INPE) kindly furnished these data. Significant differences of the mean kinetic temperature (MKT) and relative humidity (RH) for Brazilian regions were observed. These results indicate the existence of a high climatic diversity between the Brazilian regions, making challenging the definition of a single storage condition for the stability testing. Some regions present RH values higher than 80%, giving support to the concerns of the WHO, indicating the necessity of revision of existing guidelines for stability testing mainly for very hot and humid regions.

KEYWORDS Stability testing, Climatic zones, Mean kinetic temperature, Relative humidity

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INTRODUCTION

In recent years, the global pharmaceutical market has grown significantly, mainly in developing regions. In general, these countries do not have sufficient technology and industries to manufacture required significant proportions of their essential drugs. As a result, imports hold the major market of

these countries (Risha et al., 2003). Many of these new markets are located in tropical and equatorial regions, presenting hot and humid climates. The quality of the imported drugs may be adversely affected if their formulations have not been optimized for stability under the climatic conditions prevailing in these zones, causing unacceptable losses in drug efficacy (inadequate shelf-life determination). The use of suitable storage conditions for the stability testing is the best way to avoid the occurrence of these problems.

WHO and other regulatory bodies have raised concerns on the harmonization of climatic conditions for evaluation of the stability of essential drugs especially for very hot and humid regions. WHO has organized meetings to discuss "stability studies in a global environment" where recommendations for revisions of the existing WHO guidelines on stability testing have been proposed. However, the acceptance of the WHO recommendations for the industry is not yet obligatory.

This work presents a review of the methodology for determination of the storage conditions for the stability testing according to Schumacher/Grimm. The methodology was applied for the determination of the storage conditions for stability testing in the Brazilian regions and the results analyzed comparatively with the guidelines of the WHO and Brazilian regulatory agency. Brazil, a developing tropical country with huge territory and varying climate, present significant importance for the global pharmaceutical market. Therefore, the conclusions obtained in this study may be extended to other regions with similar climate and, possibly could contribute to the definition of the conditions for manufacture, storage, packing and shipment of drug products for the new markets located in hot and humid regions.

STABILITY OF DRUG PRODUCTS

Almost all drug products undergo physicochemical degradation. The extent of the degradation depends on many factors, such as storage conditions, product stability and packing material. One consequence of drug product degradation is that the preparation does not maintain the required potency over the shelf-life. Moreover, different compounds of a drug product could interact through exposure to high temperatures and humidity. These interactions could affect significantly the physical state of the drug and may generate toxic substances (Florence & Attwood, 2003). Undesirable effects of high temperatures and humidity (prevailing in tropical and equatorial climates) on biopharmaceutical properties of drugs have also been reported in the literature (Bahu & Pandit, 1997; Hogerzeil et al., 1991; Nazerali et al., 1996; Mathews, 1999; Pandit et al., 1997; Risha et al., 2002, 2003; Saville, 2001).

Physical and Chemical Deteriorative Product Changes During Storage

During the storage of drug products, several deteriorative changes can arise including physical state modifications and chemical reactions between compounds of the medicine or with external species, like oxygen. Spontaneous physicochemical state changes during storage result in a decrease in the free energy of the drug product, i.e., $\Delta G < 0$ (exergonic reaction). Once the thermodynamic equilibrium has been attained, only reversible processes can take place. However, physical chemical changes could yet occur beyond the equilibrium ($\Delta G > 0$). Positive ΔG is a characteristic of endergonic reactions and requires input of thermal energy from the environment (Hüttenrauch, 1987). In a general way, a system is more stable when the free energy variation of a drug product is higher (less negative) between the beginning and the end of the storage.

The stability of a pharmaceutical product may be affected by several factors including the physical and chemical properties of the active ingredients; the potential of interaction between active and so-called inactive ingredients of the dosage form; the container/closure system; the environmental conditions encountered during shipment, storage, and handling; and the length of time between the manufacture and usage. Environmental properties such as heat, light and moisture, as well as chemical factors including the decomposition pathways, drug solubility, pK_a, melting point, presence or absence of polymorphic crystals and hygroscopic nature of the drug could play vital roles in drug stability. The results of stability testing are used to generate stability information, which guarantee that drug products will preserve their quality, efficacy and safety up to the end of the expiration date (Hüttenrauch, 1987; Young, 1990; Grimm, 1993). The expiry date is defined as the time interval in which the preparation will remain stable when stored under the recommended conditions. Thus an expiry date is the date beyond which it is predicted that the product may no longer retain requirements for use (Kommanaboyina

& Rhodes, 1999). Temperature is the most important factor that can be involved in drug degradation and cannot be controlled by package selection (Kommanaboyina & Rhodes, 1999).

World Climatic Zones and Storage Conditions for the Stability Testing

In 1972, Futscher and Schumacher proposed that the world could be divided into four zones based on temperature and humidity, namely zone I (temperate climate), zone II (subtropical and Mediterranean climates), zone III (hot, dry climate) and zone IV (hot, humid climate). Storage conditions for stability testing were recommended for each zone (I: 21°C/45% RH; II: 25°C/60% RH; III: 30°C/35% RH; IV: 30°C/70% RH). The mean annual temperature (measured in open air) and the mean annual partial pressure of water vapor are the main criteria used for the inclusion of a region to the correct climatic conditions. According to these criterions the world was divided in four main climatic zones (Table 1).

If the climatic conditions of a city or area are incorrectly estimated, the storage conditions chosen for stability testing are often wrong. If the batches are stored under incorrect conditions, the results from the tests are also incorrect and false conclusions are drawn. Either an unstable drug product comes onto the market or, more often, stable drugs are unnecessarily discarded (Grimm, 1993). During the stability test, drug products are stored in controlled relative humidity and temperature and the results obtained support the specification period for storage, distribution, trade and use. The storage conditions recommended for each area are derived from its environmental conditions. The methodology commonly used to define the storage conditions for stability testing is outlined as follows.

Definition of Storage Conditions for Stability Testing From Climatic Data

Essentially, the definition of the storage conditions for the stability testing in a determined region is based on the mean kinetic temperature (MKT) and the relative humidity (RH). The MKT is a single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various cycles of higher and lower temperatures (WHO, 2004a). The MKT takes into account seasonal and daily temperature variation during a year. It expresses the cumulative thermal stress undergone by a product at varying temperatures during storage and distribution (Taylor, 2001).

The concept of MKT can be applied in order to provide assurance that the actual storage conditions will not affect adversely the stability and shelf-life of the product (Taylor, 2001). The use of the MKT instead of the mean arithmetic temperature is recommended when the differences between the two temperatures is higher than 5°C. This is because the temperature dependency is not linear but logarithmic according to the Arrhenius equation (Grimm, 1998).

The temperature dependence for the degradation of drug products is based on principles of chemical kinetics, specifically from Arrhenius equation:

$$\ln K = \ln A + \frac{\Delta E}{RT} \quad (1)$$

where,
K=degradation rate/s;
A=frequency factor/s;
ΔE= activation energy, (kJ/mol);
R=universal gas constant, (0.00831 kJ/mol.K);
T=absolute temperature, (K).

TABLE 1 **Criteria and Ranges for Assignment of a Region to Climatic Zones (Grimm, 1986, 1993)**

	Criterions and ranges		
Climatic zones	Mean annual temperature	Calculated mean annual temperature*	Mean annual partial pressure of water vapor
I	Up to 15°C	Up to 20.5°C	Up to 11 mbar
II	>15–22°C	>20.5–24°C	>11–18 mbar
III	>22°C	>24°C	Up to 15 mbar
IV	>22°C	>24°C	>15 mbar

*Measured temperatures lower than 19°C were set to 19°C, in the calculation of the mean annual temperature.

Based on Arrhenius equation, Haynes (1971) derived the following equation to calculate the MKT, relating the degradation rate constants at different temperatures to the activation energy (Grimm, 1993):

$$T_{MKT} = \frac{\Delta E / R}{-\ln \frac{e^{-\Delta E/RT_1} + e^{-\Delta E/RT_2} + \ldots\ldots\ldots + e^{-\Delta E/RT_n}}{n}} \quad (2)$$

where;
T_{MKT}=mean kinetic temperature, (K);
n=number of temperatures collected, (−);
T=absolute temperature, (K)

The relative humidity (RH) is the ratio of the water vapor pressure of the environment to the saturation water vapor pressure at fixed temperature. The relative humidity can be calculated from the partial and saturation pressures of the water vapor, according to Eq. (3) (Stull, 1988):

$$UR = \frac{P_D}{P_S} \times 100 \quad (3)$$

The partial and saturation pressures of the water vapor could be estimated through Eqs. (4, 5) (Stull, 1988; Peixoto & Oort, 1992):

$$P_S = 0.61078 \times \exp\left(\frac{17.269 \times T}{T + 237.3}\right) \quad (4)$$

$$P_D = 0.61078 \times \exp\left(\frac{17.269 \times T_D}{T_D + 237.3}\right) \quad (5)$$

where,
P_S=saturation pressure of the water vapor, (kP_a);
P_D=partial pressure of the water vapor, (kP_a);
T=measured environment temperature, (°C);
T_D=dew point temperature, (°C).

The storage conditions could be derived from Eqs. (2, 3). The storage conditions used generally should include a safety margin for temperature and RH.

Nowadays, the WHO has undertaken strong efforts, along with ICH and other regulatory bodies aiming to harmonize the requirements for stability evaluation of essential drugs. These concerns are fully justified since the results of these investigations are used to assign labeling that should accurately reflect the stability of the substances/products under the climatic conditions encountered in the region of distribution and use (Grimm, 1993).

The definition of the storage conditions for stability testing of essential drugs especially in very hot and humid climates (zone IV countries) is the object of enormous controversies (WHO, 2004b; ICHQ1F, 2004). Several proposed amendments in the WHO guidelines for stability testing have been considered, for example, the changing of the storage conditions for problematic regions and the addition of a new climatic zone like IVb (30°C/75% RH) comprising of very hot and humid regions.

The main reason for the controversies resides in the method used for derivation of the recommended storage conditions for stability testing, generally based on average values of temperatures and humidity of a limited number of cities. Thus, it is not surprising that large areas of the countries sampled, which may experience higher extremes of temperature and humidity, are not adequately covered by the recommended storage conditions. Moreover, storage facilities are likely to be less protective in developing countries, especially in rural areas (WHO, 2004b). Badly conditioned storage facilities may mitigate the lower extremes of temperature but not the higher ones.

Thus, mainly for the developing countries situated in very hot and humid climates, the derivation of storage conditions from climatic data representative of the local environmental conditions may support the definition of suitable storage conditions for stability testing. If more drastic storage conditions than that currently adopted were obtained, the stability testing should be performed in the new conditions in order to guarantee the patients' safety. It is evident that costs may be added to the products. To exemplify, the Brazilian situation, a huge tropical country with varying climate, important for the global pharmaceutical market will be examined in the following section.

EXAMINATION OF THE BRAZILIAN SITUATION

Evaluation of current storage conditions for stability testing in Brazil is justified due to its climatic diversity and important participation in the world pharmaceutical market. Despite stagnating pharmaceutical sales over the last years, Brazil is the tenth largest market in the world and the second largest in

Latin America after Mexico. Including the hospital market, the pharmaceutical trade in Brazil touched US$ 5.2 billion in 2002 (Palmeira Filho & Pan, 2003; Oliveira, 2003). Drugstores, the main place where Brazilian people buy their medicines, invoiced about US$ 8 billion in 2000 (Saab & Ribeiro, 2001).

Brazil has a huge territory ranging from latitudes of +5°16′20″ to –33°44′32″ and longitudes of –34°47′30″ to –73°59′32″, totaling a territory area of 8,514,876,599 km^2. Due to its geographical localization and the vast extension, the Brazilian climate is complex. In the north region prevails the typical very hot and humid equatorial climate. The tropical climate predominates in the northeast and center-west regions. The climate changes to subtropical in the southeast region and to temperate in the south. The Brazilian population is higher than 170,000,000 inhabitants (IBGE, 2000), with 7.6% living in the north region, 28.1% in the northeast region, 6.9% in the central west region, 42.6% in southeastern region and 14.8% in the south region. Although its climate varies, Brazil is included in climatic zone IV as a whole. According to this classification, the storage conditions used for stability testing in Brazil were established.

In order to evaluate the adequacy of the storage conditions currently recommended, the MKT and mean RH for Brazil and for its regions were calculated from daily data of temperature and humidity measured during 5 years. The calculated MKT and RH values were used to derivate storage conditions for stability testing in the Brazilian regions according to the methodology presented previously. The results were compared with the storage conditions proposed by the ICH (2004) for countries located in climatic zone IV and by the Brazilian National Health Surveillance Agency (Brasil, 2002; 2004; 2005).

Although, it is recommended in the label of almost all drug products sold in Brazil to store at temperatures below 30°C, maintaining this condition is seldom possible. However, a great number of daily temperatures above 30°C are observed during the year and it is difficult to control the temperature during storage in the consumer's house. Thus, the number of days with temperatures over 30°C was also determined for all investigated cities.

Obtaining the Climatic Data

Daily values of dry and dew point temperatures of all Brazilian capitals from 1998 to 2002 (5 years), collected in the morning (9 a.m.), in the afternoon (3 p.m.), and at night (9 p.m.) were kindly provided by the Brazilian Center of Weather Forecast and Climatic Studies of the National Institute of Spatial Research (CPTEC/INPE). The Brazilian capitals were chosen as source of the data due to the significant part of Brazilian population living in these zones (23% of total Brazilian inhabitants) and to its climatic heterogeneity as well. Due to the scarce data points available for the capital of the Tocantins state (Palmas), data from Porto Nacional, a representative city of this state, was used. The Brazilian map (Fig. 1) presents the states and the cities investigated. Through the study of the mean kinetic temperature, RH values and the number of days presenting temperature extremes (>30°C), storage conditions for the stability testing in the Brazilian regions could be derived.

Considering that each measured temperature prevails for 8 h, the number of full days with temperatures above 30°C for the Brazilian cities could be estimated (number of measured temperatures/3 days). Table 2 presents the results obtained for Boa Vista (Roraima state), a typical city of the north region (very hot and humid).

It can be seen in Table 2 that Boa Vista presents an extreme climatic condition, with high temperatures observed practically through most of the year. This is a typical result for the North, Northwest and Center-West regions and in many other cities located in Southwest and South of Brazil. The shipment and storage of drug products in this zone could produce high thermal stress, which can cause the drug degradation before its expiry date.

Table 3 presents the calculated values of annual mean kinetic temperature (MKT), the number of days with temperatures exceeding 30°C and the annual mean relative humidity (RH) for all Brazilian cities studied. The results confirm the high climatic diversity between the Brazilian regions, making the selection of a single condition for stability testing in Brazil challenging. High temperatures prevail throughout year in the North and Northeast regions, whereas mild temperatures are observed in South Brazil.

The calculated MKT and RH results show that the studied cities could be included in climatic zone IV. According to Grimm (1993, 1998), the stability testing for the determination of shelf-life of drug products inside climatic zone IV should be performed at 30°C and 70% RH. This storage condition was also

FIGURE 1 **Brazilian Territory, States and Studied Cities.**

recommended by the Brazilian National Health Surveillance Agency (ANVISA) until November of 2004 (Brasil, 2002) when it was altered to 30 ± 2°C/65 ± 5% (Brasil, 2004). In July of 2005, a new storage condition for stability testing in Brazil (30 ± 2°C/75 ± 5% RH), was established by ANVISA (Brasil, 2005). These continuous amendments in the Brazilian regulations probably are a result of the concerns of the WHO, ICH and others regulatory bodies on the harmonization of climatic conditions for evaluation of the stability of essential drugs especially in hot and humid regions. The current storage condition for stability testing established by the Brazilian agency was one of the proposals for revisions of the WHO guidelines debated in the Geneva meeting "*stability studies in a global environment*" for markets with very humid conditions (WHO, 2004b). It also reflects the unanimous decision of the meeting

TABLE 2 **Number of Days With Temperature Above30°C for Boa Vista in the Northern Region of Brasil**

City	Year	Temperatures above 30°C (days)	Temperatures between 30–32°C (days)	Temperatures between 32–35°C (days)	Temperatures above 35°C (days)
Boa Vista	1998	106.33	39.33	57.67	9.33
	1999	73.66	32.33	34.67	6.67
	2000	82.67	32.33	40.33	10.90
	2001	98.67	37.33	38.00	23.33
	2002	110.01	41.00	46.34	22.67

TABLE 3 **Summary of the Calculated Values of MKT, Number of Days With Temperatures Above 30°C and the Annual Mean RH for All the Brazilian Cities Studied**

Brazilian regions	Cities	Population* (inhabitants)	MKT (°C)	RH (%)	No. Days T >30°C
North	Boa Vista - RR	200,568	28.87	77.69	94.27
	Macapá - AP	283,308	28.67	80.46	74.13
	Manaus - AM	1,405,835	28.10	84.04	75.75
	Porto Nacional - TO	44,991	28.58	68.08	71.13
	Belém - PA	1,280,614	28.09	82.39	74.84
	Porto Velho - RO	334,661	28.00	80.16	73.34
	Rio Branco - AC	253,059	26.16	86.61	48.33
Mean	-	3,803,036	28.07	79.92	73.11
Northeast	São Luiz – MA	870,028	28.14	80.11	58.25
	Teresina – PI	715,360	30.06	68.14	11.83
	Fortaleza – CE	2,141,402	27.96	73.37	45.17
	Natal – RN	712,317	28.81	76.9	44.00
	João Pessoa – PB	597,934	28.27	73.83	41.67
	Recife – PE	1,422,905	27.93	74.46	45.00
	Aracaju – SE	461,534	27.71	75.56	31.00
	Salvador - BA	2,443,107	26.93	78.86	24.83
Mean	-	9,364,587	28.23	75.15	50.22
Center-west	Campo Grande – MS	663,621	25.65	67.61	45.00
	Goiânia – GO	1,093,007	26.93	60.29	59.67
	Cuiabá – MT	483,346	28.72	74.99	89.75
	Brasília - DF	2,051,146	23.66	62.76	3.58
Mean	-	4,291,120	26.24	66.41	49.50
Southeast	Vitória – ES	292,304	26.00	73.78	27.67
	Belo Horizonte – MG	2,238,526	23.86	63.20	11.25
	Rio de Janeiro – RJ	5,857,904	25.16	87.47	29.02
	São Paulo - SP	10,434,252	21.81	72.40	8.17
Mean	-	18,822,986	24.21	74.21	19.03
South	Curitiba – PR	1,587,315	23.51	84.81	15.34
	Florianópolis – SC	342,315	22.3	80.47	60.00
	Porto Alegre – RS	1,360,590	21.73	75.28	13.67
Mean	-	3,290,220	22.51	80.19	11.67
Brazil		169,799,170	27.12	76.40	47.00

*IBGE (2002).

"*Amazon countries position regarding long term stability conditions in WHO guidelines for zone IV*", to join efforts with regulatory bodies from Asian countries to request WHO to change guidelines for storage conditions for long term stability studies in zone IV towards 30°C and 75% RH.

The comparison between the changed storage conditions for stability testing obtained in this work with

recent Brazilian recommendations of ANVISA are presented in Table 4 (Brasil, 2002, 2004, 2005). It can be observed that the calculated MKT values for Brazil as well as for the Brazilian capitals (Table 3) were lower than the storage temperature, T_S, recommended for zone IV region and adopted by ANVISA. Nonetheless, the established storage conditions for the stability testing must reproduce the measured data of temperature and air humidity and should include a safety margin. The results of Table 4 give a safety margin of 2.9°C confirming the consistency of the temperature values currently used for stability testing in Brazil.

However, temperatures above 35°C are reached in Brazil during a large period of the year (Table 3). A mean of 44 days with temperatures above 30°C was observed during the year. In order to cover possibly organoleptic and physicochemical changes, the drug products should be stored at temperatures above 30°C. Grimm (1993) suggested the storage of the product at 40°C for 90 days, in order to cover the organoleptic changes for a shelf-life of 2 years. This recommendation is in accordance with the results of this work and can be done in Brazil. Furthermore, 40°C has a good safety margin since the number of days in Brazil with temperatures above 40°C is insignificant. Storing the drug products at 40°C during six months can securely reproduce in the stability testing the extremes of temperatures observed during the year in Brazil (Grimm, 1998).

On the other hand, the determined RH value (76.4%) was higher than the established value for the climatic zone IV, and significantly superior than the values recommended by ANVISA until 2004 and, in the vicinity of the actual RH value adopted (75%). Additionally, as presented in Table 3, most Brazilian regions present RH values higher than 80%. At higher RH, drugs absorb more moisture from the environment. In this situation, the substance on the surface of the solid drug product behaves as a solute. With time more water is absorbed and more drug is dissolved (Carstensen, 1995). For this reason, higher RH will be harmful to the stability of solid dosage forms, especially for very hygroscopic drugs. Thus, the results reported in this work must be considered during the selection of the packing material, which should protect the product from water absorption.

CONCLUSION

Nowadays, the global pharmaceutical market has increased significantly, with expressive contribution in the developing countries. In general these countries do not have sufficient technology and industries to manufacture drugs as per their requirements and is covered by imports. Since many of these new markets are located in hot and humid regions, the establishment of storage conditions for stability testing representing the climatic conditions prevailing in these zones is extremely necessary, in order to avoid unacceptable losses in drug efficacy. The definition of the storage conditions for stability testing of essential drugs in very hot and humid climates (zone IV countries) is the subject of much controversy (WHO, 2004b; ICHQ1F, 2004). The derivation of storage conditions from climatic data representative of the local environmental conditions where the product will be marketed may support the definition of suitable storage conditions for stability testing.

Brazil, a huge tropical country with varying climate, important for the global pharmaceutical market, is a representative example of the new market located in tropical and equatorial zones (very hot and humid climates). Significant differences in the mean kinetic temperature (MKT) and relative humidity (RH) for the Brazilian regions were observed. These results indicate the existence of a high climatic diversity between the Brazilian regions and make the definition of a single storage condition for the stability testing challenging. The temperature currently used (30°C) is adequate for

TABLE 4 **Comparison Between the Calculated Storage Conditions Obtained in the Present Work with Recent ANVISA Recommendations (Brasil, 2002, 2004, 2005)**

Calculated climatic conditions				Storage conditions					
				2002		2004		2005	
T_{mean} (°C)	MKT (°C)	RH (%)	P_D (mBar)	T_S (°C)	RH (%)	T_S (°C)	RH (%)	T_S (°C)	RH (%)
26.5	27.1	76.4	26.0	30	70	30	65	30	75

stability testing in Brazil. Nevertheless, the experimental values of relative humidity (76.4%) are significantly higher than the values recommended by ANVISA until 2004 and, in the vicinity of the actual RH value adopted (75 %). Some regions present RH values greater than 80%, giving support to the concerns of the WHO and indicating the necessity of revising existing guidelines for stability testing mainly, for hot and humid regions.

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