DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(20), 2795-2830 (1993)

STORAGE CONDITIONS FOR STABILITY TESTING IN THE EC, JAPAN AND USA; THE MOST IMPORTANT MARKET FOR DRUG PRODUCTS

W. Grimm

Department of Pharmceutical Development, Dr. Karl Thomae GmbH,
D-7951 Biberach, Germany. Thomae belongs to Boehringer Ingelheim.

ABSTRACT

Strong efforts have been undertaken to harmonise the requirements for the investigation of the stability of drug substances and drug products. Since the results of these investigations are used to assign labelling which properly reflects the stability of the substances/products under the climatic conditions encountered in the region of distribution and use, a thorough examination of the climatic conditions in the EC, Japan and the USA was conducted. According to this study, the EC, Japan and the USA may be practically assigned to a region for which there is an annual mean kinetic temperature of up to 25 degrees C.

In fact, the climatic study indicates that 25 degrees C/60 per cent RH is general well above the mean kinetic temperature for the 35 major European, Japanese and American cities in the study. In addition the mean kinetic temperature encompasses the data in warehouses as well as measured seasonal and daily fluctuations up to and above the extreme temperature of 30 degrees C allowed by the USP definition of controlled room temperature. Based upon the above, it can therefore be concluded that long term controlled room temperature labelling for

the USA, Japan and the EC can be accurately assigned by applying storage condition of 25 degrees C/60 per cent RH.

Since the applied procedure to calculate and derive climatic conditions is based on the Arrhenius equation in the modified version of Hayne's relates mainly to chemical stability. In order to follow also organoleptic and physico-chemical changes storage at higher conditions is necessary for up to 6 months (40°C/75 %) if a shelf live of at least three years is anticipated.

The described procedure and derived storage conditions allow considerably savings in capacity and cutting costs.

INTRODUCTION

Stability testing is performed to ensure that drug products retain their full efficacy up to the end of their expiration date. The results of the investigations are used to formulate the stability information which ensures the quality, efficacy and safety of the drug product.

The stability information is the product of thorough investigations and is derived from a large quantity of generated data. The basis for this is a systematic development (1) in a logically structured and optimally coordinated system. By this means the state of knowledge can be continuously extended and deepened.

12 principles (2) can be identified which are decisive for stability testing and which are applicable to all stages of development on all dosage forms.

The 12 principles are as follows:

- systematic development
- selection of batches and samples
- test criteria
- analytical methods
- specifications

- storage conditions
- testing intervals
- storage period
- number of batches
- packaging materials
- evaluation
- statements.

It is obvious that batches for stability testing have to be representative for the product in terms of composition, manufacture and packaging. The analytical methods must be stability specific, validated and the apparatus used calibrated. The storage conditions must be selected with the same care.

People very often overestimate the climatic conditions of the city or the area where they live, with the result that the storage conditions chosen for stability testing are often wrong. And if the batches are stored under incorrect conditions then 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 than not stable drugs are unnecessarily discarded.

It is necessary to exercise great caution when investigating the climatic condition in a country in a climatic zone and then derive the corresponding storage conditions.

Temperature and humidity determine storage conditions. Both factors greatly affect the stability of a drug product. As soon as a drug product is due for launch in different countries it is time to consider the climatic conditions in these countries. For this reason, the world has been divided into 4 climatic zones (3) to one of each countries can be assigned. The zones are characterised as follow with the corresponding storage conditions (2).

The selection of the different cities for the four climatic zones is done by the criteria and guide values given in table 2 (4).

TABLE 1

Definitions and storage conditions for the 4 climatic zones.

climatic zone	definition	storage condition
I	temperate climate	21°C/45 % r.h.
II	subtropical and 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.

TABLE 2

Criteria and guide values for assignment of a city to the correct climatic zone.

criteria	guide values 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, temp. < 19°C set to 19°C	up to 20.5°C	> 20.5 - 24°C	> 24°C	> 24°C
mean annual partial pressure of water vapour	up to 11 mbar	> 11 - 18 mbar	up to 15 mbar	> 15 mbar

Suitable packaging material must also be selected according to the different climatic conditions in the climatic zones.

About 85 % of the trade in drug products in the world is undertaken within the areas of the EC, Japan and the USA. Therefore thorough investigation is necessary to see whether these territories can be covered by one storage condition. When deriving storage conditions daily and seasonal climatic variations have to be considered. Furthermore the organoleptic, physico-chemical, chemical and microbial criteria of a drug product must be evaluated.

Equations and calculations

Equations

Temperature and humidity determine the climatic conditions.

The influence of the temperature on the chemical stability of a drug substance in a drug product can be described very accurately by applying the laws of reaction kinetics.

In 1889 Arrhenius described the temperature dependence of the rate of degradation by the following equation:

$$\ln k = \ln A + \frac{\Delta E}{RT}$$

Haynes (5) derived a formula from the Arrhenius equation by which the mean kinetic temperature can be calculated, allowing a single storage temperature to be determined which takes seasonal and daily temperature variations into account.

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

T_{mkt}: Mean kinetic temperature in K

ΔE: Heat of activation (activation energy) in $kJ \cdot mol^{-1}$ for which $83\ kJ \cdot mol^{-1}$ can be used.

Kennon (6) calculated the mean value for $\Delta E = 83.04\ kJ \cdot mol^{-1}$ (81 references, covering the literature from 1950 - 1964).

Grimm (7) covering the literature from 1964 - 1980 (51 references) calculated $\Delta E = 82.8$.

The overall mean value is 82.97 $kJ \cdot mol^{-1}$. Therefore 83 $kJ \cdot mol^{-1}$ represents the mean value out of 132 references.

T_{1-n}: Temperatures in K, for which the mean kinetic temperature is to be determined.

The correlation between the vapour pressure of water and the absolute temperature is given by the Clausius-Clapeyron equation, which may be written in generalised form as:

$$\ln P = -\frac{\Delta Hv}{R} \cdot \frac{1}{T} + \text{constant}$$

where ΔHv is the molar (latent) heat of evaporation.

To calculate the relative humidity the following equation is applied:

$$\text{rel. humidity} = \frac{P_D}{P_S} \cdot 100$$

P_S = saturation pressure
P_D = partial pressure

Data for the partial and saturation pressure of water are listed in (8).

The temperature dependence of permeation, diffusion and solubility of water vapour pressure through and in plastic packaging material is described by the following equations (9):

$$P = Po \cdot e^{-\Delta E_P/RT}$$
$$D = Do \cdot e^{-\Delta E_D/RT}$$
$$S = So \cdot e^{-\Delta H_S/RT}$$

Where:

$\Delta E_P/RT$ = Activation energy for permeation

$\Delta E_D/RT$ = Activation energy for diffusion

$\Delta H_S/RT$ = Head of dissolution of the gas in the plastic.

Calculations

Influence of temperature on the degradation rate

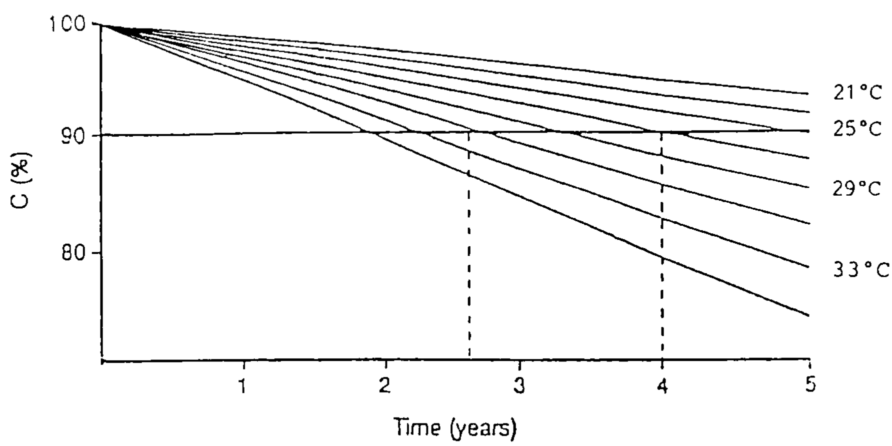

FIGURE 1: Dependence of content of drug on storage temperature.

Influence of temperature on relative humidity

TABLE 3

Dependence of changes in r.h. on temperature at a constant partial pressure of 6.1 mbar.

temperature (°C)	0	5	10	15	20	25	30	35	40	45	50
r.h. (%)	100	70	50	36	26	19	14	11	8	6.4	4.9

Calculation of storage conditions

Statements regarding the climatic conditions prevailing in the different locations can be made very precisely and reliably, since measured values for temperature and relative humidity or water vapour partial pressure, representative of a period of up to 50 years, are available for many cities throughout the world (10 - 13).

The climatic data were measured in the open air, whereas drug products are stored indoors. It is recognised that most storage rooms will be provided with some heating to compensate for low external climatic temperatures. Consequently 19°C is used as the temperature for all months during which the temperatures measured in the open are below 19°C [Haynes (5) used 17°C instead of 19°C], 21°C will be used instead of 19°C to calculate storage temperature in household medicine cabinets.

In the USA the term "controlled room temperature (CRT)" is used to describe temperatures in the 15°C to 30°C range prevailing in such diverse thermostatically maintained environments as pharmacies, hospitals and warehouses. This country-specific peculiarity is another factor to be taken into consideration.

Thus the calculation uses with 19°C a boundary temperature condition which can be significantly higher than the measured climatic value, but is considered to be more scientifically rigorous.

If the difference between temperatures is $\leq$ 5°C, the arithmetic mean temperature can be calculated. If the difference between temperatures is > 5°C the mean kinetic temperature should be calculated, applying Haynes (5) equation.

Examples:

25°C, 30°C	arithmetic mean temp.:	27.5°C
	mean kinetic temp.:	27.8°C
20°C, 40°C	arithmetic mean temp.:	30°C
	mean kinetic temp.:	34.4°C.

Table 4

Measured and calculated data for Atlanta for 3 months.

	January 7 a.m.	January 2 p.m.	May 7 a.m.	May 2 p.m.	July 7 a.m.	July 2 p.m.
measured in the open	2.9°C 79 % r.h.	11.1°C 59 % r.h.	15.1°C 83 % r.h.	26.1°C 54 % r.h.	21.5°C 90 % r.h.	30.6°C 64 % r.h.
19°C used	19°C	19°C	19°C			
calculated	19°C/32 % r.h.		22.6°C/59 % r.h.		26.1°C/75 % r.h.	

Temperature and humidity are usually measured in the open at 7 a.m. and 2 p.m. These data are taken (19°C is used for temp. below 19°C) and used to calculate mean temperature and relative humidity at this mean temperature. The procedure is shown in table 4, with data from Atlanta for January, May and July. The calculated values are for the three individual months given.

In stability testing the drug product will be kept in storage rooms at constant temperature over many months or years. It is therefore important to calculate the data over the entire year.

The measured and calculated data for Atlanta for one year read as follows:

measured data		calculated data amt*		calculated data mkt*	
16.3°C	14.3 mbar	21.5°C	56 % r.h.	21.7°C	55 % r.h.

* arithmetic mean temperature, mean kinetic temperature

TABLE 5

Calculation for Phoenix (USA) using 19°C and 30°C for the months May and July.

	May		July	
	7 a.m.	2 p.m.	7 a.m.	2 p.m.
measured in the open	13.9°C 37 % r.h.	33.8°C 13 % r.h.	23.9°C 47 % r.h.	40.3°C 20 % r.h.
19°C and 30°C used	19°C	30°C		30°C
calculated arithmetic mean temperature	24.5°C/21 % r.h.		27.0°C/41 % r.h.	
mean kinetic temperature	26.0°C		27.4°C	

30°C is the upper CRT limit given in the USP for the storage of drug products. Therefore 30°C will be used (besides 19°C) for all data above 30°C for cities in the USA. It is therefore assumed that the air conditioning is not very effective and the temperature is only lowered to 30° degrees C.

The mean daily maximum for Phoenix exceeds 30°C in May, June, July, August, September, October. Taking that this temperature prevails 4 hours a day, we can calculate the number of full days (where day = a unit comprising 24 hours and 30 days = 1 month) with a temperature of 30°C in Phoenix as follows:
4 hours x 30 days x 6 months = 720 hours/24 hours = 30 days.

If the drug products are stored in Phoenix for 12 months at CRT without air conditioning, this would be equivalent to 30 days continuous storage at 30°C, to cover this extreme temperature.

If the drug products were stored in a household medicine cabinet, without air conditioning and not considering the storage instruction, to store below 30°C, the calculation for Phoenix looks like this (table 6):

TABLE 6

Calculated data for Phoenix using 21°C for household medicine cabinet for the months May and July.

	May		July	
	7 a.m.	2 p.m.	7 a.m.	2 p.m.
measured in the open	13.9°C 37 % r.h.	33.8°C 13 % r.h.	23.9°C 47 % r.h.	40.3°C 20 % r.h.
21°C used	21°C			
calculated arithmetic mean temperature	27.4°C/18 % r.h.		32.1°C/30 % r.h.	
mean kinetic temperature	29.4°C		35.1°C	

Calculated data in the USA

In table 7, data are summarised for cities of climatic zone I in the USA. Selection according to table 2.

In the table 8, data are summarised for cities of climatic zone II in the USA.

Cities in the USA with climatic conditions above climatic zone II are summarised in table 9.

These data are well below these of climatic zones III and IV, see tables 13 and 14.

TABLE 7
Cities of climatic zone I in the USA

city	measured data			calculated data		4 hottest months			
	temp. [°C]	partial pressure [mbar]	temp. 19°C used [°C]	rel. humidity [%]	partial pressure [mbar]	[°C]			
Albuquerque	13.7	6.5	21.4	26	6.5	26.0	25.2	25.1	23.5
Boston	10.8	9.9	20.1	42	9.9	23.4	22.9	21.8	21.0
Buffalo	8.2	9.0	20.0	39	9.0	22.9	22.5	21.5	20.5
Chicago	10.5	9.9	20.4	41	9.9	24.3	23.5	22.7	21.4
Columbus (Ohio)	11.0	10.9	20.8	44	10.9	24.7	24.2	23.6	22.2
Denver	9.7	7.4	20.7	30	7.7	25.2	24.8	23.4	22.6
Detroit	10.1	9.2	20.3	39	9.2	23.9	23.4	22.6	21.2
Madison	7.3	9.1	20.1	39	9.1	23.5	22.9	22.0	20.5
New York	12.5	10.7	20.6	44	10.7	24.9	23.9	22.0	21.6
Omaha	10.8	10.8	21.0	43	10.8	25.8	24.8	23.6	23.0
Philadelphia	11.9	10.5	20.6	43	10.5	24.5	23.9	23.3	22.1
Pittsburgh	10.2	9.6	20.4	40	9.6	23.8	23.4	22.8	21.6
Portland	7.2	8.5	19.8	37	8.5	22.7	22.4	21.0	20.1
Providence	10.1	9.3	20.1	40	9.3	23.2	22.9	21.8	21.0
Salt Lake City	10.5	6.8	21.2	27	6.8	26.8	25.9	23.9	23.0
San Francisco	13.8	11.5	19.1	52	11.5	19.8	19.6	19.0	19.0
Seattle	10.6	9.7	19.6	43	9.7	21.6	21.4	20.0	19.9
St. Louis	13.0	10.3	21.1	41	10.3	25.6	24.9	24.3	23.2
mean	10.7	9.4	20.5	39	9.4	24.0	23.5	22.5	21.6

TABLE 8

Cities of climatic zone II in the USA.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C, 30°C used [°C]	calculated data rel. humidity [%]	calculated data mean kinetic temp. [°C]	calculated data days per annum with 30°C
Ashville	12.6	12.0	20.7	49	20.8	0
Atlanta	16.3	14.3	21.5	56	21.7	10
Birmingham	17.8	16.0	22.0	61	22.4	20
Charleston	18.5	16.3	22.1	61	22.4	15
El Paso	17.3	7.8	22.1	29	22.5	25
Houston	21.1	18.3	22.9	66	23.2	20
Kansas City	13.7	12.2	21.3	43	21.5	10
Las Vegas	18.7	6.0	22.3	22	22.7	25
Little Rock	16.5	14.7	21.8	56	22.1	20
Los Angeles	18.0	13.0	21.2	52	21.6	0
Nashville	15.6	12.3	21.0	49	21.8	15
New Orleans	21.3	19.7	22.9	71	23.2	20
Oklahoma	15.8	13.6	21.7	52	21.9	15
Phoenix	20.6	8.8	23.0	31	23.5	30
Sacramento	15.7	10.9	21.5	43	21.8	20
San Diego	17.4	14.2	20.5	59	20.6	0
Washington	13.9	13.0	21.7	50	22.0	5
mean	17.1	13.0	21.7	50	22.0	15

TABLE 9
Cities in the USA with climatic condition above climatic zone II.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C, 30°C used [°C]	calculated data rel. humidity [%]	calculated data mean kinetic temp. [°C]	calculated data days per annum with 30°C
Hilo	22.8	21.5	23.2	76	23.9	-
Honolulu	24.4	21.8	24.4	71	24.9	-
Miami Beach	24.5	22.0	24.5	71	24.9	15
San Juan	25.8	25.6	25.8	77	26.1	5
Tampa	22.4	19.8	23.6	67	24.1	25
mean	24.0	22.1	24.3	72	24.8	9

Calculated data in the EC

TABLE 10
Cities of climatic zone I in the EC.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C used [°C]	calculated data rel. humidity [%]	calculated data partial pressure [mbar]	4 hottest months [°C]			
Amsterdam	10.3	10.5	19.3	47	10.5	20.3	20.3	19.6	19.0
Berlin	11.0	10.0	19.6	44	10.0	21.4	21.2	20.7	19.3
Bolzona	12.0	10.7	20.4	45	10.7	23.6	23.2	22.5	21.8
Bordeaux	12.5	12.3	20.0	53	12.3	22.4	22.2	21.4	21.1
Brussels	11.9	10.7	19.4	48	10.7	20.7	20.6	19.9	19.3
Copenhagen	10.0	9.5	19.2	43	9.5	20.4	19.4	19.0	19.0
Dresden	9.2	9.7	19.6	43	9.7	21.5	21.4	20.8	19.5
Dublin	11.6	10.6	19.0	48	10.6	19.3	19.2	19.0	19.0
Frankfurt	10.7	9.7	19.8	42	9.7	21.9	21.7	21.2	19.9
Hamburg	8.7	9.3	19.3	55	9.3	20.7	20.5	19.8	19.0
London	12.1	10.0	19.2	45	10.0	20.2	19.7	19.0	19.0
Luxembourg	8.8	9.7	19.4	43	9.7	20.9	20.6	20.1	19.0
Lyons	13.9	10.8	20.1	46	10.8	23.4	23.1	21.6	20.8
Marseilles	14.2	11.3	20.5	47	11.3	24.0	23.7	22.6	22.1
Munich	10.4	9.1	19.5	40	9.1	21.1	20.9	20.2	19.3
Paris	13.5	10.2	19.8	44	10.2	22.1	21.6	21.0	20.1
Strasbourg	10.0	10.4	19.7	45	10.4	21.9	21.6	21.0	19.9
Stuttgart	9.7	9.1	19.6	40	9.1	21.5	21.4	20.8	19.5
Toulouse	12.7	12.1	20.1	51	12.1	22.9	22.9	21.7	21.4
mean	11.2	10.3	19.6	45	10.3	21.5	21.4	20.6	19.9

TABLE 11

Cities of climatic zone II in the EC.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C used [°C]	calculated data rel. humidity [%]	calculated data mean kinetic temp. [°C]	calculated data days per year with temp. above 30°C
Athen	18.3	12.5	21.5	48	22.2	10
Barcelona	16.5	14.4	20.6	59	20.6	0
Cadiz	18.1	15.6	20.8	64	20.9	0
Gibraltar	18.5	15.2	20.8	62	21.0	0
Heraklion	18.6	14.2	21.3	65	21.5	0
Lisbon	16.6	13.5	20.6	56	20.6	0
Madrid	13.9	10.1	20.6	42	20.7	5
Malaga	18.5	15.2	21.2	60	21.3	0
Messina	18.0	15.0	21.2	60	21.4	5
Naples	16.4	13.7	20.9	56	21.0	0
Palermo	18.2	13.2	21.2	52	21.4	10
Rome	16.2	14.8	20.9	49	21.1	10
Saloniki	16.1	13.0	21.4	51	21.7	10
Seville	18.8	11.6	21.3	58	23.2	20
mean	17.3	13.8	21.0	55	21.3	5

Calculated data in Japan

TABLE 12

Cities of climatic zone II in Japan.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C used [°C]	calculated data rel. humidity [%]	calculated data mean kinetic temp. [°C]	calculated data days per year with temp. above 30°C
Hiroshima	14.8	13.7	21.0	55	21.1	5
Nagasaki	16.5	15.0	21.3	59	21.8	5
Osaka	15.5	14.3	21.4	56	21.6	10
Tokyo	14.5	13.8	20.9	56	21.0	5
mean	15.3	14.2	21.2	56	21.4	6

One city in Japan (Naha Okinawa/with climatic data above climatic zone II

city	measured data temp. [°C]	partial pressure [mbar]	calculated data temp. 19°C used [°C]	rel. humidity [%]	mean kinetic temp. [°C]	days per year with temp. above 30°C
Naha	22.2	21.5	23.0	77	23.2	5

Calculated data in climatic zone III

TABLE 13

Cities of climatic zone III.

city	measured data temp. [°C]	partial pressure [mbar]	calculated data temp. 19°C used [°C]	rel. humidity [%]	mean kinetic temp. [°C]	days per annum with temp. above 40°C
Aswan	27.0	10.0	28.3	25.4	30.0	
Baghdad	22.7	11.0	25.7	33.6	27.0	15
Elat	25.0	12.0	26.4	34.9	28.3	5
Khartoum	29.5	11.8	29.9	28.0	32.5	
Mossul	20.2	12.0	24.5	39.0	25.7	10
New Delhi	24.8	14.5	26.8	41.0	27.9	5
Riyadh	24.9	8.0	26.7	22.8	28.0	20
Suez	22.5	13.5	24.4	44.2	25.4	
Jerusalem	22.8	14.5	24.6	46.9	25.8	0
mean	24.4	11.9	26.4	34.6	27.9	

Calculated data in climatic zone IV

TABLE 14

Cities of climatic zone IV.

city	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C used [°C]	calculated data rel. humidity [%]	calculated data mean kinetic temp. [°C]	calculated data days per annum with temp. above 30°C
Bangkok	28.1	28.6	28.1	75.1	29.1	60
Belem	26.6	32.2	26.6	92.4	27.6	55
Bombay	26.9	27.0	26.9	76.0	27.6	35
Darwin	28.1	24.0	28.1	63.1	29.1	60
Jakarta	26.8	27.9	26.8	80.0	27.4	35
Calcutta	26.3	25.5	26.3	74.0	27.0	40
Manila	28.2	28.0	27.2	77.3	28.2	50
Maracaibo	29.0	28.5	29.7	73.0	31.0	60
Recife	26.3	15.8	26.3	75.3	26.7	0
Rio de Janeiro	23.0	22.0	23.3	77.0	23.8	0
Singapore	27.3	28.2	27.3	77.7	27.9	55
Taipei	22.1	21.0	23.4	73.0	23.8	20
mean	26.5	26.6	26.7	76.0	27.4	40

Measured and calculated data in warehouses of the four climatic zones (14)

TABLE 15

Measured and calculated data in warehouses of the four climatic zones.

climatic zone	cities with the warehouses	measured data in warehouses [°C]	measured data in warehouses [% r.h.]	calculated data for cities with warehouses [°C]	calculated data for cities with warehouses [% r.h.]	calculated data for climatic zone [°C]	calculated data for climatic zone [% r.h.]
I	Harlem, Hattenheim, Vevey	18.7	45.3	19,6	46.0	20	42.0
II	Barcelona, Buenos Aires, Istanbul, Madrid, Mexico City, Santiago de Chile, Seville, Sydney, Tokyo	21.1	58.0	21.1	55.9	21.4	53.0
III	New Delhi, Khartoum	26.0	53.5	28.4	35.0	26.4	35.0
IV	Abidjan, Bangkok, Bombay, Caracas, Columbo, Dacca, Madras, Rio de Janeiro, Singapore	28.4	70.0	26.4	75.0	26.7	76.0

Annual and daily temperature pattern of the four climatic zones

The seasonal temperature variations in the four climatic zones can be described as follows (16):

TABLE 16

Annual temperature pattern in the four climatic zones.

climatic zone	annual temperature pattern	mean kinetic temperature
I	19°C/8 months, 23°C/3 months, 25°C/1 month	20.8°C
II	21°C/6 months, 26°C/4 months, 30°C/2 months	25.1°C
III	25°C/4 months, 30°C/4 months, 34°C/4 months	30.3°C
IV	27°C/4 months, 29°C/4 months, 31°C/4 months	29.1°C

For the hot and hottest months the daily temperature pattern was calculated as follows (16):

TABLE 17

Daily temperature pattern with the extreme temperatures during the hot and hottest months in the four climatic zones.

climatic zone	temperature/ time	daily temperature pattern 8 h	6 h	4 h	6 h	mean kinetic temperature
I	23°C/3 months 25°C/1 month	20°C 20°C	22°C 24°C	26°C 31°C	24°C 26°C	22.7°C 25.1°C
II	26°C/4 months 30°C/2 months	21°C 24°C	25°C 28°C	31°C 36°C	27°C 32°C	26.1°C 29.9°C
III	30°C/4 months 34°C/4 months	24°C 25°C	28°C 32°C	36°C 42°C	32°C 36°C	29.9°C 34.2°C
IV	29°C/4 months 31°C/4 months	26°C 26°C	28°C 28°C	32°C 35°C	30°C 32°C	28.7°C 30.9°C

Finally the permissible extreme temperatures per annum still covered by the recommended storage temperatures in the 4 climatic zones were calculated:

TABLE 18

Permissible extreme temperatures in the four climatic zones.

climatic zone	storage temperature	extreme temperature covered per year
I	21°C	26°C/22 days 31°C/ 5 days
II	25°C	36°C/10 days 32°C/15 days 31°C/20 days
III	30°C	42°C/20 days 36°C/50 days
IV	30°C	35°C/20 days 32°C/50 days

Discussion

Comparison of measured and calculated data in the USA, the EC and Japan and the comprehensive storage conditions

In the three areas a number of cities have been investigated and assigned to the climatic zone I or II.

These data will now be compared.

Data of climatic zone I:

TABLE 19

Mean values of cities in climatic zone I for the USA, the EC and Japan.

area	measured data temp. [°C]	measured data partial pressure [mbar]	calculated data temp. 19°C used [°C]	calculated data rel. humidity [%]
USA $\bar{x}_{18}$	10.7	9.4	20.5	39
EC $\bar{x}_{19}$	11.2	10.3	19.6	45
Japan x_1	7.6	9.8	19.7	42
$\bar{x}_{38}$	10.9	9.9	20.9	42

For Japan data are only available for Sapporo whereas for the USA and the EC the figures are representative.

The data are in good agreement indicating that climatic and storage conditions are comparable.

Table 20

Mean values of the cities in climatic zone II for the USA, the EC and Japan.

area	measured data		calculated data				
	temp. [°C]	partial pressure [mbar]	temp. 19°C,30°C* used [°C]	mean kinetic temp. [°C]	rel. humidity [%]	days per annum 30°C*	days per annum above 30°C
USA $\bar{x}_{17}$	17.1	13.0	21.7	22.0	50	15	
EC $\bar{x}_{14}$	17.3	13.8	21.0	21.3	55		5
Japan $\bar{x}_4$	15.3	14.2	21.2	21.4	56		6
$\bar{x}_{35}$	17.0	13.5	21.4	21.7	53		

* CRT in USA only

In climatic zone II the measured and calculated data also show a good agreement for the three areas. One difference must be mentioned. Due to the CRT in the USA the temperature can not exceed 30°C, inlike in the EC and Japan, as shown in table 20.

Since the climatic conditions, measured and calculated, are in good agreement the same storage condition can be applied in the USA, the EC and Japan.

In the following the storage condition for climatic zone II is compared with the measured and calculated data of climatic zone II representing 35 cities.

measured data in climatic zone II		calculated data in climatic zone II			derived data for climatic zone II		
temp. [°C]	partial pressure [mbar]	temp. [°C]	mean kinetic temp. [°C]	rel. humidity [%]	temp. [°C]	partial pressure [mbar]	rel. humidity [%]
17	13.5	21.4	21.7	53	25	19	60

The climatic values will probably vary symmetrically with the following limits:

25°C ± 2°C   60 % ± 5 %

The derived storage conditions of climatic zone II is well above the calculated data, allowing safety margin for the temperature of 3.3°C and for the partial pressure of 5.5 mbar.

Comparison of measured and calculated data for warehouses shows that, again (see table 15), agreement is excellent:

measured data in warehouses of climatic zone II temp. [°C]	rel. humidity [%]	calculated data for the storage conditions in the warehouses temp. [°C]	rel. humidity [%]
21.1	58	21.1	56

These data show two important facts:

- the procedure to calculate storage conditions from measured data is well established
- the measured data in warehouses are well below the storage conditions for climatic zone II, giving proof of the safety margin.

In table 21 the number of days per annum with 30°C in the USA and above 30°C in the EC and Japan are presented. They are compared with the allowable extreme temperatures in climatic zone II (table 18).

TABLE 21

Comparison of number of days per annum, 30°C in the USA, > 30°C in the EC and Japan with allowable days > 30°C in climatic zone II.

area	number of days with 30°C		number of days above 30°C		allowable days in climatic zone II with temperatures above 30°C 10 days 36°C, 15 days 32°C, 20 days 31°C ≙ 45 days > 30°C
	maximum	average	maximum	average	
USA	30	15			45
EC	-	-	15	5	45
Japan	-	-	10	6	45

The safety margin is 30 days (minimum 15 days), in the USA, 40 days (minimum 30 days) in the EC and 39 days (minimum 35 days) in Japan.

This demonstrates very clearly the safety margin inherent in the storage conditions of climatic zone II (25°C/60 %).

With regard to

- calculated storage conditions of climatic zone II
- measured and calculated storage conditions in warehouses
- measured extreme temperatures.

The investigations of the climatic conditions in the three areas have shown that most cities can be assigned to the climatic zones I and II.

Cities in the USA with climatic conditions above climatic zone II are summarised in table 9. These include Florida, Puerto Rico and Hawaii, 6 % of the population of the USA.

The mean kinetic temperature for these cities is 24.8, just below the storage temperature of 25°C. That means even this part of the USA is covered by the storage condition for climatic zone II. In the EC all parts are within climatic zones I and II, Okinawa in Japan (1 % of the population) does not fall under zone I and II. Here, the mean kinetic temperature is 23°C, which is still well below 25°C.

To sum up:

The climatic conditions in the USA, the EC and Japan are quite similar with comparable data for the investigated cities in the climatic zone I and II. In the USA 94 % of the population lives in the climatic zone I and II, in the EC 100 %, in Japan 99 %.

All areas in climatic zone II in the three territories can be covered by one storage condition (thereby naturally including climatic zone I as well) 25°C/60 % r.h.

The storage condition includes - with plenty of room to spare - the measured and calculated data from cities (35) and warehouses in climatic zone II, has a safety margin allowing for permissible extremes of temperature, and is even sufficient to cover the kinetic mean temperature in cities with climatic conditions exceeding those of climatic zone II.

Storage conditions for a registration application in the EC, Japan and the USA

The derived storage condition for climatic zone II and the other zones is based on Haynes version of the Arrhenius equation and as such is mainly concerned with the chemical and microbial stability for which the laws of reaction kinetics are applicable. However the organoleptic and physico-chemical criteria also have to be considered.

Therefore it is necessary to store the sample not only at 25°C/60 % but also for a fixed period of time at higher storage conditions.

TABLE 22

Storage period and conditions to cover organoleptic and physico-chemical test criteria for an anticipated shelf life of 3 years.

area	storage temperature [°C]	average number of days [days]	maximum number of days [days]	storage conditions [months]	[°C] [% r. h.]
USA	30	45	90	3	30/60*
EC	> 30	15	45	1 1/2	40/75*
Japan	> 30	18	30	1	40/75*

* Only necessary when plastic packaging materials are used (non tight containers)

According to table 21 the following number of days per annum with 30°C in the USA and above 30°C in the EC and Japan have been identified:

USA: 30°C: average 15 days, maximum 30 days
EC: > 30°C: average 5 days, maximum 15 days
Japan: > 30°C: average 6 days, maximum 10 days

For an anticipated shelf life of three years the average or maximum days per annum have to be multiplied by 3 (table 22).

In the USA with CRT 30°C would be sufficient as accelerated temperature to cover organoleptic and physico-chemical test criteria. In the EC and Japan 30°C can be exceeded therefore a higher temperature, 40°C, is necessary.

To harmonise the accelerated storage conditions, 40°C/(75 % r.h.) will be used for the three areas of the EC, Japan and the USA. Then also extreme temperatures which may arise also in the USA during shipment are included.

If the accelerated storage condition [40°C/(75 % r.h.)] will not only be used to cover organoleptic and physico-chemical test criteria but also to make prediction of the chemical and microbial stability the storage period may be extended to 6 months.

Therefore the following storage conditions for a registration application in the EC, Japan and the USA are necessary.

Storage condition	storage period	
accelerated storage 40°C (75 % r.h.)	up to 3 months to cover organoleptic and physico-chemical test parameter, including shipment	up to 6 months including prediction of chemical and microbial stability
long term testing 25°C/60 %	12 months for marketing application	3 to 5 years up to the end of the shelf life

For some products an alternative accelerated storage condition to 40°C/(75 % r.h.) may be required. 30°C/NLT 60 % r.h. has been mentioned in the stability guideline and samples would be stored under these condition when:

- irreversible change takes place at 40°C
  - inhomogenity of semi-solids
  - phase-separation of semi-solids
  - melting of suppositories
- results do not comply with specifications
  - discoloration
  - increase dissolution rate
  - decrease in hardness
  - change, increase of particle size in suspension.

Evaluation of stability data to derive tentative shelf lives for the EC, Japan and the USA

After 12 months storage data are filed for a marketing application.

A tentative shelf life of up to 2 to 3 years is anticipated, therefore predictions are necessary.

The chemical and microbial stability (analysis of the preservative) can be calculated from the results of the samples stored at 40°C/75 % r.h. The Arrhenius equation is applied, $\Delta E = 83\ kJ \cdot mol^{-1}$, the specifications are fixed to $\leq$ 5 % as fall in assay or increase in degradation products. The specification for the preservative may be fixed to $\leq$ 10 %.

Generally speaking, the following statement can be made concerning organoleptic and physico-chemical changes with the different dosage forms.

TABLE 23

Calculated shelf lives for the chemical stability of drug products stored at 40°C/(75 %).

storage temp. [°C]	storage period [months]	% decom-position [%]	% of decrease in content or % decomposition at 25°C			shelf live at 25°C [years]
			1 year	2 years	3 years	
40	3	5	3.9	7.6	-	1
40	3	3	2.4	4.8	7.1	2
40	6	5	2.0	4.0	6.0	2
40	6	3	1.2	2.4	3.6	$\geq$ 3

TABLE 24

Expected organoleptic and physico-chemical change of the different dosage forms stored at accelerated conditions.

dosage form	storage condition	organoleptic changes	physico-chemical changes
solid dosage forms	3 months 40°C/75 %	none	none
	6 months 40°C/75 %	possible	possible
	6 months 30°C/60 %	none	none
semi solid dosage forms	3 months 40°C/75 %	possible	possible
	6 months 40°C/75 %	expected	expected
	6 months 30°C/60 %	none	none
liquid dosage forms	3 months 40°C/75 %	none	none
	6 months 40°C/75 %	possible	possible
	6 months 30°C/60 %	none	none

In table 25, examples are given covering all test criteria and including the labelling.

As shown in table 25, the data of assay and decomposition for storage at 25°C/60 % r.h. may be included.

Labelling requirements differ in the USA, the EC and Japan. In the USA labelling is generally necessary.

TABLE 25

Examples of stability results and the evaluation to propose shelf live.

storage conditions	organoleptic and physico-chemical test criteria	chemical test criteria*	microbial test criteria when necessary**	tentative shelf life climatic *zone II*	labelling
3 months 40°C/(75 %)	within specifications	5 % decomposition	> 12 % decomposition	1 year	USA: CRT (15-30°C) EC, Japan none
12 months 25°C/60 %	within specifications	~ 4 % decomposition	~ 10 % decomposition		
3 months 40°C/75 %	within specifications	3 % decomposition	≤ 6 % decomposition	2 years	USA: CRT (15-30°C) EC, Japan none
12 months 25°C/60 %	within specifications	~ 2 % decomposition	~ 5 % decomposition		
6 months 40°C/75 %	within specifications	5 % decomposition	≤ 12 % decomposition	2 years	USA: CRT (15-30°C) EC, Japan none
12 months 25°C/60 %	within specifications	~ 2 % decomposition	~ 5 % decomposition		
6 months 40°C/75 %	within specifications	3 % decomposition	~ 8 % decomposition	≥ 3 years	USA: CRT (15-30°C) EC, Japan none
12 months 25°C/60 %	within specifications	~ 1 % decomposition	~ 3 % decomposition		
3 months 40°C/75 %	out of specifications	3 % decomposition	≤ 6 % decomposition	2 years	USA: CRT (15-30°C) EC, Japan store at up to 30°C
3 months 30°C/60 %	within specifications	~ 1 % decomposition	~ 2 % decomposition		
12 months 25°C/60 %	within specifications	~ 2 % decomposition	~ 5 % decomposition		

* Fall in assay or decomposition ≤ 5 % as specification

** Fall in assay or decomposition ≤ 10 % as specification

According to the USP, draft definition drug products stored at 25°C/60 % as the mean kinetic temperature for the CRT (15 - 30°C) may be labelled for storage at controlled room temperature (between 15°C and 30°C).

If the results of samples, stored for 3 months at 40°C/75 % and for 12 months are all within specification, labelling in the USA will be store at controlled room temperature (15 - 30°C).

In the EC and Japan no labelling is necessary.

If the results after 3 months at 40°C/75 % are outside specifications but within specifications after 3 months at 30°C/60 %.

Labelling is necessary for the USA, the EC and Japan. The CRT in the USA must also be guaranteed during shipment.

Temperature and humidity determine storage conditions, both factors affect the stability of a drug product if the packaging material is not watertight.

Strictly speaking, a shelf life prediction from storage under accelerated conditions is only possible, if the sorption behaviour is comparable for solid dosage forms under the different conditions. Therefore it is strongly recommended to investigate the sorption behaviour in an open container at 25°C/60 %, 30°C/60 %, 40°C/75 %.

It would be a big mistake to only increase the temperature and disregard humidity when testing the extremes (30°C in the USA, > 30°C in the EC, Japan). The following table shows the relative humidities calculated for a number of cities in the USA when the temperature is raised to 30°C.

Krummen (15) showed very clearly that raising of the temperature without a corresponding increase in rel. humidity falsifies prediction. Samples stored at 35°C/< 40 % r. h. were nearly as stable as samples stored at 21°C/60 % r.h.

TABLE 26

Calculated rel. humidity for a number of cities in the USA when the temperature is raised to 30°C.

city	temp. [°C]	partial pressure [mbar]	rel. humidity [%]
Chicago	30°C	9.9	23
Philadelphia	30°C	10.5	25
Pittsburgh	30°C	9.6	23
Atlanta	30°C	14.3	34
Houston	30°C	18.3	43
New Orleans	30°C	19.7	46

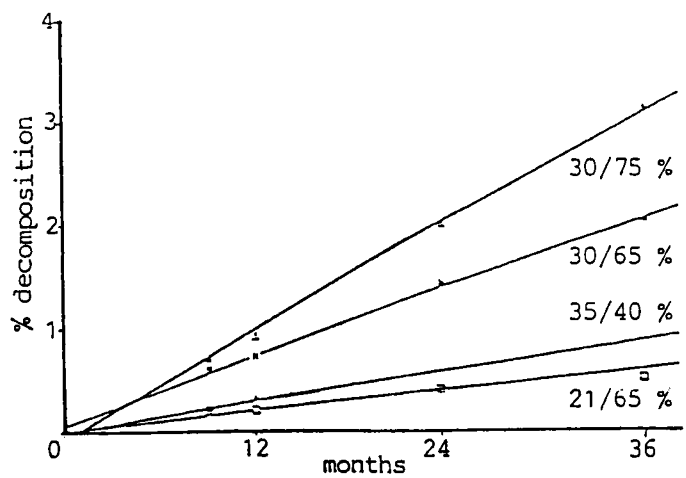

Figure 2: Decomposition of drug substance in tablets in relationship to the storage conditions.

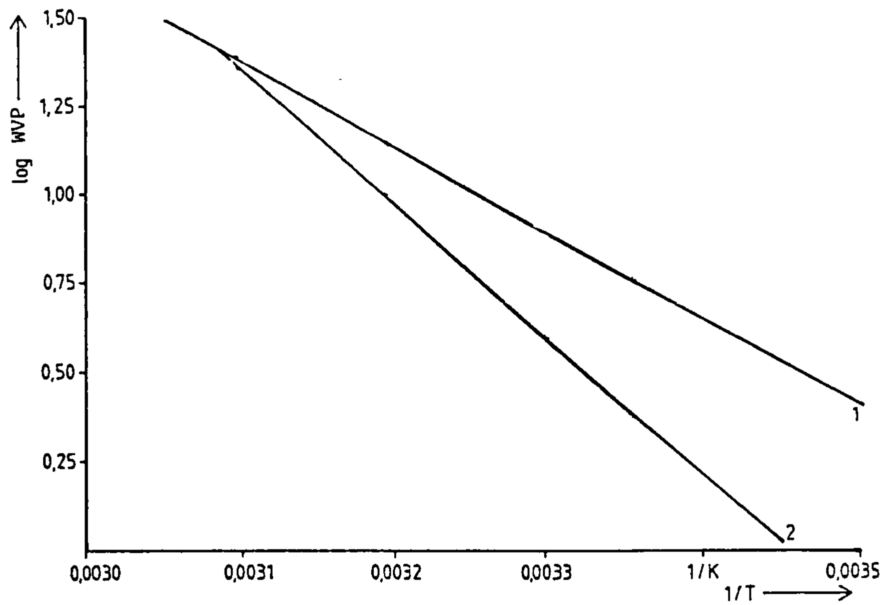

Figure 3: Temperature dependence of water vapour permeability through plastic materials log WVP = f (1/T), WVP (G/m² x 24 h), 1: polytherephthalate, 2: polyethylene.

Furthermore the temperature dependence of the water vapour permeability through plastic materials has to be considered (7)

To ensure the quality, efficacy and safety of a drug product with worldwide distribution:

- corresponding storage conditions are necessary
- different shelf lives are derived
- different packaging materials may be necessary

SUMMARY

Strong efforts are being undertaken to harmonise the requirements for the investigation of drug products with the aim of saving capacity and cutting costs.

Important progress has been reached especially in the field of stability testing within the three territories the EC, Japan and the USA.

Uniform storage conditions are a basic requirement. Therefore, a thorough investigation into the climatic conditions in the EC, Japan and the USA was conducted.

The world can be divided into four climatic zones. According to the results of the investigation the EC, Japan and the USA can be assigned to climatic zones I and II.

In the EC 100 % of the population live in climatic zone I and II, in Japan 99 % and in the USA 94 %. Combining climatic zone I and II, one storage condition was derived 25°C/60 % r.h. The mean kinetic temperature of 25°C covers also those areas in the USA and Japan with climatic condition above zone I and II.

The derived storage condition has been compared with the calculated data for 35 cities in the three areas with data measured in warehouses. It had been made sure that seasonal and daily fluctuation were included.

For the EC, Japan and the USA the number of days per annum with temperature at 30°C (USA) and temperatures above 30°C (EC and Japan) were also calculated.

The derived storage condition (25°C/60 %) is well above the calculated data for 35 cities, data measured in warehouses, includes seasonal and daily fluctuations and covers very well the extreme temperatures of 30°C and above.

Since the applied procedure to calculate and derive climatic conditions is based on the Arrhenius equation it relates mainly to the chemical stability. In order to follow also organoleptic and physico-chemical changes storage at higher condition is necessary for up to three months if a shelf life of at least three years is anticipated.

Due to the controlled room temperature in the USA, the storage temperature cannot exceed 30°C which is likely in the EC and Japan.

However temperatures above 30°C may also be reached in the USA during shipment.

These eventualities are covered by the storage at 40°C/75 % for three months.

If under these storage conditions irreversible changes take place or results of organoleptic or physico-chemical test parameters are outside specifications samples are stored at 30°C/60 % instead.

In the following tables the various data are summarised.

The data in tables 27 and 28 prove the margin of safety inherent in the storage condition for climatic zone II (25°C/60 %) taking into account calculated data for 35 cities, measured data in 9 warehouses and extreme temperatures. Even the cities in the USA and Japan with calculated data above climatic zone II are covered.

Finally it has been demonstrated how shelf life predictions can be made that include all test criteria.

TABLE 27

Measured and calculated data in the three areas of the climatic zone II.

	temp. [°C]	partial pressure [mbar]	rel. humidity [%]
measured data in the open for 35 cities	17.0	13.5	70
calculated data for these 35 cities	21.4	13.5	53
measured data in 9 warehouses	21.1	14.5	58
calculated data for the corresponding 9 cities	21.1	14.0	56

TABLE 28

Number of days per annum with high temperatures calculated and covered by the storage temperature of 25°C.

area	number of days with 30°C in the USA and above 30°C in the EC and Japan maximum	average	allowable days with temperature above 30°C but covered by 25°/60 %
USA	30	15	45
EC	15	5	45
Japan	10	6	45

TABLE 29

Comparison of arithmetic mean temperatures and mean kinetic temperatures.

	arithmetic mean temperature	mean kinetic temperature
Calculated data climatic zone II	21.4°C	21.7°C
Calculated data of cities in the USA above climatic zone II	24.3°C	24.8°C
Calculated data of cities in Japan above climatic zone II	22.2 °C	23.2 °C
15 - 30°C (CRT)	22.5°C	25.1°C

Thus it can be concluded: stability testing in the EC, Japan and the USA can be performed applying the same storage conditions. The derived storage conditions, 25°C/60 % for long term testing and 40°C/75 % for high temperatures contain a safety margin, meaning that the derived shelf lives also have a built in safety margin.

References

1. PMA's joint PDS stability committee "Stability Concepts", Pharmaceutical Technology, June 1984
2. W. Grimm; K. Krummen; in Stability Testing in the EC, Japan and the USA, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart (1993)
3. N. Futscher; P. Schumacher; Pharm. Ind. 34, 479 - 483 (1972)
4. W. Grimm; Drugs made in Germany 28, 196 - 202 (1985) and 29, 39 - 47 (1986)
5. J.D. Haynes; J. Pharm. Sci. 60, 927 - 929 (1971)
6. L. Kennon; J. Pharm. Sci 53, 815 - 818 (1964)
7. W. Grimm; G. Schepky; in Stabilitätsprüfung in der Pharmazie, Theorie und Praxis, page 200; Editio Cantor Verlag, Aulendorf (1980)
8. Smithsonian Meteorological Tables, 6th ed. Smithsonian Institution, Washington (32) (1966)
9. A. Martin, et al.; Physical Pharmacy, Lea a. Febiger, Philadelphia (1983)
10. Länder und Klima Europa/UDSSR, F.A. Brockhaus, Wiesbaden (1982)
11. Länder und Klima, Nord- und Südamerika, F.A. Brockhaus, Wiesbaden (1982)
12. Länder und Klima, Asienl/Australien, F.A. Brockhaus, Wiesbaden (1982)
13. Länder und Klima, Afrika, F.A. Brockhaus, Wiesbaden (1982)
14. E. Spingler, Verpackungs-Rundschau 3, 17 - 21 (1974)
15. K. Krummen; in Migration bei Kunststoffverpackungen, APV Paperback, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, page 94 (1988)
16. W. Grimm; Drug Develop. Ind. Pharmacy, 12, 1259-1292 (1986)