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RESEARCH PAPER

Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV

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ABSTRACT

The International Conference on Harmonization (ICH) Tripartite Guideline "Stability Testing of New Drug Substances and Products" sets out the stability testing requirements for a registration application within the three areas of the European Union, Japan, and the United States. These areas are assigned to climatic zone II with the storage condition of 25°C/60% RH. This paper describes the adjustments that are necessary to extend the guideline to countries of climatic zones III and IV.

At first storage conditions were derived with 30°C/35% RH for climatic zone III and 30°C/70% RH for climatic zone IV. Both conditions contain a margin of safety compared to calculated and measured data in warehouses. Furthermore, they cover the extreme temperatures above 30 and 40°C which may arise in these climatic zones. Six months at 40°C/75% RH was fixed as storage condition for accelerated testing to assess organoleptic and physicochemical test criteria and to make predictions for chemical stability. The predictive factor is 3.3 for 30°C (6 months at 40°C corresponds to 20 months at 30°C). Extreme temperatures which may arise during shipment are covered by the results of stress investigations (e.g., 3 months at 50°C).

The next adjustment is necessary for the selection of the packaging containers. They must reflect the requirements for solid, semisolid, and liquid dosage forms caused by the two storage conditions. In the evaluation the temperature difference of 10°C (40–30°C) instead of 15°C has to be considered, which limits the preliminary shelf lives in critical cases to 18 months instead of 24 months. Finally,

statement/labeling must reflect the storage conditions. All of the other basic principles for the drug substances and drug products, such as selection and number of batches, test criteria, test procedures, specifications, testing frequency, and storage period can be applied without any change.

INTRODUCTION

The International Conference on Harmonization (ICH) Tripartite Guideline "Stability Testing of New Drug Substances and Products" defines the stability testing requirements for a registration application within the three areas of the European Union, Japan and the United States. These areas are assigned to climatic zone (CZ) II with the storage condition of 25°C/60% RH. The application of the guideline can be extended to all other countries within the climatic zone without any change.

The ICH Guideline does not seek to cover the testing that may be required for registration in other areas of the world with different climatic conditions. Therefore, corresponding storage conditions have to be fixed. This paper describes the extension of the ICH Tripartite Guideline and describes the stability requirements for a registration application within countries of climatic zones III and IV. The main aspect of this paper is the derivation and definition of the storage conditions for climatic zones III and IV.

STORAGE CONDITIONS FOR CLIMATIC ZONES III AND IV

To harmonize and simplify worldwide stability testing, the world has been devided into four climatic zones (1). They are characterized in Table 1 (2).

The criteria and guide values for assignment of a city to the correct climatic zone are listed in Table 2 (3).

The following countries can be assigned to the climatic zones I and II (4):

Table 1

Definition and Storage Conditions for the Four Climatic Zones

Climatic Zone	Definition	Storage Condition
I	Temperate climate	21°C/45% RH
II	Subtropical and Mediterranean climates	25°C/60% RH
III	Hot, dry climate	30°C/35% RH
IV	Hot, humid climate	30°C/70% RH

Europe: all countries.

America: Argentina, Bolivia, Chile, Canada, Mexico, Peru, Uruguay, USA.

Asia: Afghanistan, Armenia, Azerbaijan, China, Georgia, Iran, Israel, Japan, Kazakstan, Kirghizia, Korea, Lebanon, Nepal, Syria, Tadzhikistan, Turkey, Turkmenia, Uzbekistan.

Africa: Egypt, Algeria, Tunesia, Libya, Morocco, Namibia, Ruanda, South Africa, Tunesia, Zambia, Zimbabwe.

Australian: Australia, New Zealand.

For these countries the storage condition is 25°C/60% RH.

The following countries can be assigned to the climatic zones III and IV (4):

America: Barbados, Belize, Brazil, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haita, Honduras, Jamaica, Columbia, Cuba, Nicaragua, Dutch Antilles, Panama, Paraguay, Puerto Rico, Venezuela. All of these countries are assigned to CZ IV.

Africa: Angola, Ethiopia, Benin, Botswana (III), 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 (III), Uganda, Zaire, Central African Republic.

Asia: Bahrain, Bangladesh, Hong Kong, India, Indonesia, Iraq (III), Jordan (III), Kampuchea, Qatar, Kuwait, Laos, Malaysia, Maldive Islands, Myanmar, Oman, Pakistan, Philippines, Saudi Arabia, Singapore, Sri Lanka, Taiwan, Thailand, United Arab Emirates, Vietnam, Yemen

Australian/oceanic: Figi, Society Islands, Marshall Islands, New Caledonia, Papua-New Guinea, Samoa, Tonga.

The storage conditions have to be derived for these countries. The climatic conditions in a series of cities of the climatic zones III and IV have been investigated. The measured data (in the open) and calculated data were contrasted (5). Cities of climatic zones III and IV are presented in Tables 3 and 4.

Table 2

Criteria Used to Classify a Site According to 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 (<19°C)	Up to 20.5°C	>20.5–24°C	>24°C	>24°C
Mean annual water vapor partial pressure	Up to 11 mbar	>11–18 mbar	Up to 15 mbar	>15 mbar

Table 3

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. (°C)	Partial Pressure (mbar)	Temp. 19°C Used (°C)	Relative Humidity (%)	Mean Kinetic Temp. (°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

Table 4

Cities of Climatic Zone IV

City	Measured Data		Calculated Data			Days per Annum with Temp. Above 30°C	Days per Annum with Temp. Above 40°C
	Temp. (°C)	Partial Pressure (mbar)	Temp. 19°C Used (°C)	Relative Humidity (%)	Mean Kinetic Temp. (°C)		
Bangkok	28.1	28.6	28.1	75.2	29.1	60	0
Belem	26.6	32.2	26.6	92.5	27.6	55	0
Bombay	26.9	27.0	26.9	76.2	27.6	35	0
Darwin	28.1	24.0	28.1	63.1	29.1	60	0
Jakarta	26.8	27.9	26.8	79.2	27.4	35	0
Calcutta	26.3	25.5	26.3	74.5	27.0	40	0
Manila	28.2	28.0	27.2	77.6	28.2	50	0
Maracaibo	29.0	28.5	29.7	68.3	31.0	60	0
Recife	26.3	25.8	26.3	75.4	26.7	0	0
Rio de Janeiro	23.0	22.0	23.3	77.0	23.8	0	0
Singapore	27.3	28.2	27.3	77.7	27.9	55	0
Taipei	22.1	21.0	23.4	73.0	23.8	20	0
Mean	26.5	26.6	26.7	75.8	27.4	40	0

The following information relates to Tables 3 and 4.

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 designated for all temperatures below 19°C. For the corresponding calculated mean temperature the relative humidity is determined.

Mean Kinetic Temperature

If a mean temperature is calculated and the difference between two temperatures is >5°C, the mean kinetic temperature should be calculated instead of the arithmetic mean temperature. This is because the temperature dependency is not linear but logarithmic according to the Arrhenius equation. Haynes (6) derived an equation based on the Arrhenius equation to calculate the T_{mkt}, the mean kinetic temperature:

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

where ΔE is activation energy in kJ · mol^{-1} for which 83 kJ · mol^{-1} can be used (5).

For example, for 20°C and 40°C, the arithmetic mean temperature is 30°C and the mean kinetic temperature is 34.4°C.

The calculated mean kinetic temperatures are 27.8 and 27.4°C. The storage temperature for both was fixed at 30°C to include a margin of safety of 2.2 and 2.6°C, respectively. The measured, calculated, and derived data for climatic zones III and IV are summarized in Tables 5 and 6.

In the next step, measured data in warehouses (7) were compared with calculated data for warehouses in these cities and compared with the calculated mean values for the two climatic zones III and IV (see Table 7).

The following conclusions can be drawn:

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

In the next two steps, potential seasonal and daily temperature variations are calculated and summarized in Tables 8 and 9.

Table 5

Measured, Calculated, and Derived Data

	Measured Data		Calculated Data		Derived Data	
Climatic Zone	Temp. (°C)	Partial Pressure (mbar)	Mean Kinetic Temp. (°C)	Relative Humidity (%)	Temp. (°C)	Relative Humidity (%)
III	24.4	11.9	27.8	35.1	30	35
IV	26.5	26.6	27.4	75.8	30	70

Table 6

Calculated and Derived Storage Conditions and the Margin of Safety

Climatic Zone	Calculated Storage Condition		Derived Storage Condition		Margin of Safety	
	(°C)	(mbar)	(°C)	(mbar)	(Δ°C)	(Δmbar)
III	27.8	14.8	30	14.9	2.2	0
IV	27.4	27.7	30	29.7	2.6	2

Table 7

Measured and Calculated Data in Warehouses

Climatic Zone	Cities with the Warehouses	Measured Data in Warehouses		Calculated Data for Cities with Warehouses		Calculated Data for Climatic Zone	
		(°C)	(% RH)	(°C)	(% RH)	(°C)	(% RH)
III	New Delhi, Khartoum	26.0	53.5	28.4	35.0	27.8	35.1
IV	Abidjan, Bangkok, Bombay, Colombo, Dacca, Madras, Rio de Janeiro, Singapore	28.4	30.0	26.4	75.0	27.4	75.8

Table 8

Annual Temperature Pattern in Climatic Zones III and IV

Climatic Zone	Annual Temperature Pattern	Mean Kinetic Temperature
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

Table 9

Daily Temperature Pattern with the Extreme Temperatures During the Hot and the Hottest Months in Climatic Zones III and IV

Climatic Zone	Temperature/ Time	Daily Temperature Pattern (°C)				Mean Kinetic Temperature (°C)
		8 hr	6 hr	4 hr	6 hr	
III	30°C/4 months	24	28	36	32	29.1
	34°C/4 months	24	32	43	35	34.1
IV	29°C/4 months	26	28	32	30	28.7
	31°C/4 months	26	28	35	32	30.9

In Tables 3 and 4, the days per annum with temperatures above 30 and 40°C are listed. These data indicate the general difference in the climatic conditions of the zones III and IV. In climatic zone III, 10 days are above 40°C and no day is above 40°C in climatic zone IV.

From the data in Table 9, the number of days with temperature above 40°C for climatic zone III and above 30°C for climatic zones III and IV are calculated.

Table 10

Calculated Number of Days with Temperatures Above 30 and 40°C

Climatic Zone	Number of Days Above 40°C	Number of Days Above 30°C
III	20	110
IV	-	100

Table 11

Comparison of Allowable Number of Days per Annum Above 30 and 40°C

Climatic Zone	Number of Days Above 40°C		Number of Days Above 30°C		Difference Number of Days
	Real	Storage Cond.	Real	Storage Cond.	
III	10	20	–	–	10
III	–	–	24	110	86
IV	–	–	40	100	60

For example: Number of days above 40°C in climatic zone III = 4 hottest months ≙ 120 days; 4 hr/day 43°C (4 × 120)/24 = 20 days. The data are summarized in the Table 10.

A comparison of the real number of days and the number of days according to the storage temperature of 30°C is indicated in Table 11.

The difference in number of days demonstrates very clearly that all the extremes during storage and even during shipment are covered for both climatic zones by the storage temperature of 30°C. The derived storage conditions are based on Hayne's version of the Arrhenius equation and as such cover mainly the chemical and microbial stability for which the laws of reaction kinetics are applicable. To cover the organoleptic and physicochemical test criteria and also to make predictions for chemical stability, an accelerated storage condition is necessary. In the ICH Stability Guideline, 40°C/75% RH was fixed as accelerated storage condition. To standardize a worldwide stability program as much as possible, the same accelerated storage condition of 40°C/75% RH should also be applied for climatic zones III and IV.

The addition of a second accelerated storage condition such as 45°C/75% RH is not necessary and should be omitted because:

- In climatic zone IV the number of days above 40°C is 0, therefore the extremes during storage are well covered by 6 months at 40°C/75% RH.
- In climatic zone III 10 days are above 40°C, but these are accompanied by very low relative humidity; 45°C/75% RH would not be present at these climatic conditions.
- A walk-in cabinet for 45°C/75% RH would be nearly unbearable, therefore, for larger quantities, several small cabinets would be necessary.
- Because of the 15°C difference between 25 and 40°C, the predictive factor for the chemical stability is 5. The 6-month value at 40°C corresponds to the 30-month value at 25°C. For the temperature difference of 10°C (40 – 30°C), the predictive factor is 3.3. Under this precondition, the data can be used in the same way.

Furthermore, the adsorption for solid dosage form at open storage should be comparable at 30°C/70% RH and 45°C/75% RH. Because of the higher temperature at 45°C/75% RH, the drugs adsorb much less than at 30°C/70% RH.

In summary, the accelerated storage condition at 40°C/75% RH also fulfills the requirements for climatic zones III and IV. To safeguard the stability information for climatic zones III and IV, data of stress investigations during development with temperatures >40°C are always available for the drug substance and the drug product. Therefore, the extremes during shipment in these climatic zones can be well covered according to relevant data for at least 6 weeks at 50°C.

THE REMAINING BASIC PRINCIPLES

The requirements of the ICH Stability Guideline for the drug substance and the drug product are based on the following principles: selection and number of batches, test criteria, test procedures, specifications, storage conditions, testing frequency, storage period, packaging/containers, evaluation, and statements/labeling. The principles are all applicable for the extension of the ICH Stability Guideline for stability testing to countries of climatic zones III and IV besides storage conditions, partly packaging/containers, evaluation, and statements/labeling. The requirements for the storage conditions have been explained in detail and the remaining principles will be described.

Table 12

Storage Conditions for Climatic Zones III and IV

	Conditions	Minimum Time Period of Submission
Long-term testing	30 ± 2°C/70 ± 5% RH	12 months
	(30 ± 2°C/35 ± 5% RH)[a]	12 months
Accelerated testing	40 ± 2°C/75 ± 5% RH	6 months

[a]Only necessary if exclusively for climatic zone III.

DRUG SUBSTANCE

Selection and number of batches, test criteria, test procedures, specifications should be made according to ICH Stability Guideline.

Storage Conditions

The storage conditions should be sufficient to cover storage, shipment, and subsequent use. The storage conditions are as follows: climatic zone III: 30°C/35% RH; climatic zone IV: 30°C/70% RH.

The storage temperature is the same with 30°C, the relative humidity is different. If a drug substance will be applied exclusively in climatic zone III, then samples are stored correspondingly at 30°C/35% RH; if the substance is used in climatic zones III and IV, samples are stored exclusively at 30°C/70% RH (Table 12).

The accelerated storage condition is 40°C/75% RH.

For possible extreme temperatures during shipment the results of the stress testing should be considered. Usually the drug substance is stable under these storage conditions so that a significant change happens very rarely.

Testing of frequency and period of storage is according to ICH stability guideline.

Packaging/Container

The drug substances are usually stored in fiber drums lined with polyethylene films. Hygroscopic drug substances are stored in stainless steel containers lined with polyethylene foil. In climatic zone III, samples can be stored in fiber drums, even if the drug substance is hygroscopic, because of the low relative humidity. Substances should generally be shipped in stainless steel containers. Since the containers are always lined with polyethylene foil, the results of tests in fiber drums can be transferred to results from stainless steel containers. For hygroscopic drug substances stored in climatic zone IV, the stability testing should be done in tight glass containers lined with polyethylene foil.

Evaluation

Results of Stress Testing

Samples stored at 60°C with decomposition of 0.5 and 1% after 3 months correspond to the following rate of decomposition at 30°C (35 or 70% RH). For $\Delta E5$, 83 kJ · mol^{-1} was used (5) (Table 13).

For drug substances, a retest period is derived instead of a shelf life estimate. The retest period is the period of time during which the drug substance can be considered to remain within release specifications. Because

Table 13

Decomposition at 60°C and the Corresponding Data for 30°C

60°C	30°C				
3 Months	12 Months	24 Months	36 Months	48 Months	60 Months
0.5%	0.10	0.20	0.30	0.41	0.51
1.0%	0.20	0.41	0.62	0.82	1.03

Table 14

Calculated Rates of Decomposition at 40°C/75% RH and the Corresponding Data at 30°C/70% RH; All Data are Percentages

Fall in Assay or Decomposition	40°C/75% RH		30°C/70% RH								
	3 Months	6 Months	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	48 Months	60 Months
0.5	99.93	99.86	99.97	99.95	99.92	99.90	99.85	99.80	99.70	99.60	99.5
1.0	99.86	99.71	99.95	99.90	99.85	99.80	99.70	99.60	99.40	99.20	99.0
2.0	99.71	99.42	99.90	99.80	99.70	99.60	99.40	99.20	98.80	98.40	98.0
3.0	99.56	99.13	99.85	99.70	99.54	99.39	99.09	98.79	98.19	97.59	97.0
4.0	99.42	98.84	99.80	99.59	99.39	99.19	98.78	98.38	97.58	96.79	96.0
5.0	99.27	98.54	99.74	99.49	99.23	98.98	98.47	97.97	96.97	96.98	95.0

usually no decomposition takes place, regression analysis with the stability data of the registration batches is not necessary. Examples are given in Table 14.

The long-term testing of the registration batches of the drug substance covers at least 12 months at the time of submission. According to Table 14, the assay values are in the range of 99.9–98.98%. This fall in assay can be determined only by the quantitative determination of the decomposition product and not by direct analysis. The data are within the confidence limit of the analytical procedure.

The results of stress investigations at temperatures >40°C (50 or 60°C) or the results of accelerated testing with 6 months at 40°C/75% RH can be used to predict the possible decompositions up to 5 years. A retest period of 2 years will be derived with an extension up to 5 years if the data indicate no decomposition until the end of the storage of 5 years. Then the retest date is extended for 1 year annually.

With unstable drug substances it may be necessary to fix a shelf life. The corresponding specification is then the release specification for the drug product, e.g., the specification for the decomposition.

DRUG PRODUCT

Selection and number of batches, test criteria, test procedures, specifications are made according to ICH Stability Guideline.

Storage test conditions are the same as for the drug substance.

Testing of frequency and period of storage is according to ICH Stability Guideline.

Table 15

Prediction of Applicable Packaging/Containers for Climatic Zones III and IV

Dosage Form	Climatic Zone	Packaging Material
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

Table 16

Decomposition at 40°C and Prediction of Chemical Stability at 30°C; All Data are Percentages

40°C		30°C					Shelf Life
3 Months	6 Months	12 Months	24 Months	36 Months	48 Months	60 Months	(Years)
0.25	0.5	99.7	99.3	99.0	98.6	98.3	5
0.50	1.0	99.3	98.6	97.9	97.2	96.7	5
0.75	1.5	99.0	97.9	96.9	95.9	94.9	4
1.00	2.0	98.6	97.2	95.9	94.5		3
1.26	2.5	98.2	96.5	94.8			2
1.51	3.0	97.9	95.8	93.8			2
1.77	3.5	97.5	95.1				<2
2.02	4.0	97.2	94.5				1
2.28	4.5	96.8	93.8				1
2.53	5.0	96.5	93.1				1
3.00	6.0	95.8	91.7				1

Table 17

Organoleptic and Physicochemical Instability at 40°C

Storage Period at 40°C	Organoleptic or Physicochemical Change	Conclusions
3 months	Significant change	No shelf life prediction beyond storage period at 30°C possible
3 months	No significant change	Shelf life >2 years possible
6 months	Significant change	Shelf life >2 years possible
6 months	No significant change	Shelf life >3 years possible

Table 18

Storage Instructions for Drug Products in Climatic Zones III and IV

Storage Conditions	Instability	Label Statement
40°C/75% RH	Organoleptic or physicochemical instability	Do not store above 30°C
30°C/35 or 70% RH	Organoleptic or physicochemical instability	Store below 8°C
	Chemical instability	Short shelf life or store below 8°C

Packaging/Containers

Testing of unprotected drug product can form a useful part of the stress testing and package evaluation. Storage in open or unprotected containers provides valuable information for solid dosage forms. However conclusions can be drawn only if storage is done under normal 30°C/35% RH, 30°C/70% RH, or accelerated conditions at 40°C/75% RH. Because it may be very seldom that a development is done only for climatic zone III, the storage condition of 30°C/35% RH is usually not available. The samples can then be stored at 40°C without controlled humidity. This corresponds to 40°C/20–30% RH.

For the application of packaging/containers in climatic zones III and IV, the predictions shown in Table 15 can be made.

Evaluation

With a systematic development in a logically structured and optimally coordinated stability program with stress and accelerated tests during development and for the final formulation, data are available which permit a shelf-life prediction of 2–3 years before starting long-term testing with the registration batches. The results of the registration batches will then confirm the prediction. The predictions of the chemical stability from the results of samples stored at 40°C are listed in Table 16

If a significant change in chemical stability takes place after 6 months at 40°C, the drug product is very unstable anyway, because a shelf life of <2 years is generally not acceptable. If a significant change takes place concerning organoleptic or physicochemical stability, the following distinction can be made. For organoleptic and physicochemical instability, the predictions shown in Table 17 can be made.

Statement/Labeling

Labeling with storage instructions may be necessary in climatic zones III and IV under the conditions shown in Table 18.

A summary of the Extension of the ICH Tripartite Guideline for the Stability Testing of New Drug Sub-

Table 19

Extension of the ICH Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV

Basic Principle	Stress Testing with Drug Substance	Stress Testing with Drug Product	Accelerated and Long-Term Testing with Drug Substance Formal Studies	Accelerated and Long-Term Testing with Drug Product Formal Studies	On-Going Testing Accelerated and Long-Term with Drug Substance	On-Going Testing Accelerated and Long-Term with Drug Product
Selection of batches	Experimental batch	Experimental, clinical pilot-plant batches	Representative pilot-plant batches	Representative pilot-plant batches	Representative pilot-plant and production batches	Representative pilot-plant and production batches
Test criteria	Corresponding objective	Corresponding dosage forms and objective	Corresponding to influence on quality, safety, efficacy. Physical, chemical, microbiological	Corresponding to influence on quality, safety, efficacy. Organoleptic, physical, chemical, micro-biological	Corresponding to influence on quality, safety, efficacy. Physical, chemical, microbiological	Corresponding to influence on quality, safety, efficacy. Organoleptic, physical, chemical, micro-biological
Test procedures	Stability indicating, preliminary validated	Stability indicating, preliminary validated	Stability indicating, fully validated	Stability indicating, fully validated	Stability indicating, fully validated	Stability indicating, fully validated
Specifications	Preliminary release specifications	Preliminary shelf-life specifications	Release specifications	Shelf-life specifications	Release specifications	Shelf-life specifications
Storage conditions	Open, not defined, e.g., 50, 60, 70°C	Open, not defined, e.g., 50, 60, 70°C	40°C/75% RH, 30°C/70% RH, (30°C/35% RH)	40°C/75% RH, 30°C/70% RH, (30°C/35% RH)	30°C/70% RH, (30°C/35% RH)	40°C/75% RH, 30°C/70% RH, (30°C/60% RH)
Testing frequency	Open, not defined	Open, not defined	0, 3, 6, 9, 12 months	0, 3, 6, 9, 12 months	18, 24, 36, 48, 60;[a] 3, 6, 9, 24, 36,[b] 48, 60 months	18, 24, 36, 48, 60;[a] 3,6, 9, 24, 36, 48,[a] 60 months

(*continued*)

Table 19. Continued

Basic Principle	Stress Testing with Drug Substance	Stress Testing with Drug Product	Accelerated and Long-Term Testing with Drug Substance Formal Studies	Accelerated and Long-Term Testing with Drug Product Formal Studies	On-Going Testing Accelerated and Long-Term with Drug Substance	On-Going Testing Accelerated and Long-Term with Drug Product
Storage period	Open, not defined	Open, not defined	40°C/75% RH → 6 months, 30°C/70% RH → 12 months	40°C/75% RH → 6 months, 30°C/70% RH → 12 months	30°C/70% RH → 60 months, 30°C/70% RH → 60 months	30°C/70% RH → 60 months, 40°C/75% RH → 6 months 30°C/70% RH → 60 months
Number of batches	1	1	3	3	3 On-going, 3 production	3 On-going, 3 production
Packaging container	Not defined	Not defined	Final or simulate final	Final or simulate final	Final or simulate final	Final or simulate final
Evaluation	Open, not defined physical, chemical quality characterics; kinetic and statistical calculations	Open, not defined organoleptic physical, chemical, micro-biological quality characteristics; kinetic and statistical calculations	Organoleptic, physical, chemical, quality characteristics, regression analysis where reasonable	Organoleptic, physical, chemical, micro-biological quality characteristics, regression analysis where reasonable	Organoleptic, physical, chemical quality characteristics, regression analysis where reasonable	Organoleptic, physical, chemical microbiological quality characteristics, regression analysis where reasonable
Statements, labeling	Prediction of retest period, storage instructions if necessary; stability profile of drug substance	Prediction of shelf life, storage instructions if necessary; stability profile of drug product	Prediction of retest period, storage instructions if necessary	Prediction of shelf life, storage instructions if necessary	Extension and confirmation of retest period, storage instructions if necessary	Extension and confirmation of shelf life, storage instructions if necessary

[a]On-going of registration batches.
[b]Production batches.

stances and Products to Countries of Climatic Zones III and IV is shown in Table 19.

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