

or abroad, can be chosen as the reference preparations.

(3) Test procedure As described under the single dose study of Ordinary Preparations.

(4) Submission of data

a. Make tables and diagrams to show the data of plasma concentration of samples, and their mean value and standard deviation at different time obtained from each subject.

b. The individual parameters of C_{max} , T_{max} , $AUC_{0-\infty}$, $AUC_{0-\tau}$, F , and mean values, standard deviations should be calculated. Other parameters such as mean residence time (MRT) et al also should be submitted as far as possible.

c. The requirements for clinical report, side effects, and adverse reactions are required as same as that for ordinary preparations.

(5) The bioequivalence evaluation For comparison between test and reference extended, controlled release preparations, the two preparations are bioequivalent if AUC and C_{max} comply with the requirements of bioequivalence and T_{max} has no significant difference by statistical analysis. For comparison between test extended, controlled release preparations and ordinary preparations, the extent of absorption of the two preparations is bioequivalent if AUC complies with the requirements of bioequivalence (the same as AUC bioequivalence evaluation of ordinary preparations); the test preparations have the extended or controlled release character if C_{max} is reduced, T_{max} is extended, and at least one parameter in the results does not comply with the requirements of bioequivalence by statistic analysis according to part 9 described under ordinary preparations.

2. Multiple dose, two-period crossover study The objective of this study is to investigate the rate and extent of absorption, and fluctuation of blood concentration at the steady state when multiple doses of test and reference extended, controlled release preparations are given.

(1) The requirements and selection criteria for subjects

The selection of subjects is similar as described under Single dose study and the subjects used in Single dose study can be continuously selected. 18 to 24 subjects are required. If necessary, the number can be increased. Reference preparations are similar as described under Single dose study.

(2) Study design and procedure A randomized crossover study design and multiple doses administration of test and reference preparations are recommended. For test preparation, the studied out scheme of dosage and administration is used. The preparations, which are administrated once a day, should be dosed in the morning following a fast of at least 10 hours; subjects should continue fasting for 2 to 4 hours after dosing. For preparations which are dosed twice a day, the first dose should be given following a fast of 10 hours, and subjects should continue fasting 2-4 hours after dosing; the second dose should be administrated before or after the meal of 2 hours and subjects should continue fasting for 2 hours post-dose. Each dose should be administered with 250 ml of warm water. In general, subjects can drink water after 1-2 hours of dosing. When reference is ordinary preparation, the routine clinical dosage and administration is used, but the overall dosage should be equal to the dosage per day of test extended, controlled release preparations.

(3) Blood-sampling design After multiple doses are given for a period of at least 7 elimination half-lives, three trough concentrations (C_{min}) on three consecutive days should be determined to ascertain that the blood concentrations are at steady state. Blood sampling should be collected at the same time (normally in the morning) of different days in order to offset an interference of time to pharmacokinetics and be comparable. After reaching steady state and in a dosing interval of the last dose administration, adequate blood samples should be collected according to blood-sampling design of Single dose study. Then the blood concentration-

time curve data during that interval will be measured and other related parameters of pharmacokinetics, e. g., the peak drug concentration, the time for peak concentration, average drug concentration at steady state (C_{av}) and AUC^s etc. will be calculated.

(4) Pharmacokinetics data processing a. Make tablet and diagrams to show the data of plasma concentration of samples, and their mean value and standard deviation at different time obtained from each subject.

b. Individual C_{max} , C_{min} , T_{max} , C_{av} , AUC^s , and mean value and standard deviation of each parameter should be calculated. C_{max} and T_{max} are obtained directly from data without interpolation. In general, C_{min} is obtained from the average of two trough concentrations. One is sampled before a dosing during an interval of the last dose administration, and the other is sampled at the τ . AUC^s is calculated by the trapezoidal rule.

Average drug concentration at steady state (C_{av}) which can be calculated as following:

$$C_{av} = (AUC^s) / \tau$$

where AUC^s is area under the blood concentration-time curve from time zero to time τ over a dosing interval at steady state, and τ is the dosing interval.

c. Bioavailability at steady state can be calculated as follows:

$$F = (AUC^s)_T / (AUC^s)_R \times 100\%$$

$$F = (AUC^s)_T \times D_R / (AUC^s)_R \times D_T \times 100\%$$

d. Percent degree of fluctuation ($DF\%$) of blood concentration, which can be calculated as following.

$$DF = 100\% \times (C_{max} - C_{min}) / C_{av}$$

where C_{max} is peak drug concentration, obtained directly from the data, after the last dose is administrated at steady state and C_{min} is a trough concentration at the end of last dosing interval during steady state. If reference preparation is the same extended release preparation, D_T/τ of test preparation should not be more than 143% of reference preparation. If reference preparation is ordinary preparation, D_T/τ of test preparation should be significantly less than that of ordinary preparation.

e. Statistical analysis and bioequivalence evaluation The methods and requirements for statistical analysis and bioequivalence evaluation are similar as described under Single dose study of extended, controlled release preparations.

f. Clinical report, side effects, and adverse reactions The requirements are the same as that for ordinary preparations.

XX C Guidelines for the Stability Testing of Drug Substances and Preparations

The purpose of stability testing is to provide information on the quality variation of a drug substance or drug preparation with time under the influence of a variety of environmental factors, such as temperature, humidity and light, to substantiate the recommended manufacture, package, storage, transportation and shipment conditions, and to establish shelf lives of the drug concerned.

The basic requirements for stability testing include: (1) Affecting factors testing, accelerated testing and long-term testing. One batch of drug substance is required for affecting factors testing. Three batches of substance/drug preparation are required for accelerated and long-term testing. (2) Drug substances used for stability testing should be from pilot

scale, and the amount required for testing should be equivalent to that for stability testing of their preparations. The manufacturing process should be the same as those for full scale production. The drug preparations used for stability testing should be from extended pilot scale (e.g., about 10000 tablets or capsules for Tablets or Capsules, at least about 10 times the amount needed for tests of each item for large volume preparations, such as intravenous infusion, oral solution, etc., the amount of particular preparation or dosage form can be varied depending on specific conditions.), and the formulation and manufacturing process should be the same as those of full scale manufacturing. (3) The quality specification of the drug for stability testing should be identical to that for pre-clinical and clinical studies. (4) The container, packaging materials and final package of the drug for accelerated and long-term testing should be the same as those for marketing. (5) The testing methods for assessment of drug stability testing must be accurate, precise and specific for the drug substance or preparation as well as for related substances (including degradation products and other substances introduced under various environmental or product related factors), and these analytical parameters should be validated to ensure the reliability of the results of the stability testing. The determination of degradation products and related products is important in the stability testing. (6) Because the quantity of the pilot production is less than that of full scale manufacturing, the applicant shall promise that the accelerated and long-term testings are also to be conducted for the first three batches of the validated full scale manufacturing. This guideline consists of two parts; the first is for drug substance, and the second is for drug preparation.

Drug substance The following tests for drug substance should be carried out.

1. *Affecting factors testing* This testing is normally carried out under more severe conditions than those used for accelerated testing. The purpose is to investigate the intrinsic stability of the drug substance in order to identify the factors that affecting stability, and the likely degradation pathways and degradation products, so that provide the rational scientific evidence for manufacturing, package, storage of the drug preparation and establishment of the analytical method for degradation products. This testing may be carried out on sample of a single batch. The substance being examined is usually distributed evenly in a suitable container (e.g., weighing bottle or petri dish) to form a thin layer with a thickness of not more than 5 mm, or not more than 10 mm for loose substance. Where significant change in degradation products is found according to the testing result, qualitative and quantitative analysis should be conducted for the degradation products due to the potential safety problem when necessary.

(1) *High temperature testing* Open the loaded container and place it in a suitable clean and tightly closed facility at 60°C for ten days. Sampling at the fifth and the tenth day and examine the specified items of stability testing. Where the substance changes significantly (e.g., a 5% potency loses from the initial assay value), the additional testing at 40°C should be conducted.

(2) *High humidity testing* Open the loaded container and place it in a closed facility with constant humidity at 25°C/90% ± 5% RH for ten days. Sampling at the fifth and the tenth day and examine the specified items of stability testing. The weight of the substance before and after testing is weighed accurately to evaluate the hygroscopic properties of the substance. Where increase is more than 5% of its weight, additional testing at 25°C/75% ± 5% RH should be conducted. Conditions of constant humidity are made up by

placing a saturated salt solution in the lower part of the closed container, such as a desiccator. According to the requirements for relative humidity, saturated solutions of NaCl (75% ± 1% RH at 15.5°C to 60°C) and KNO₃ (92.5% RH at 25°C) may be used appropriately.

(3) *Photostability testing by strong light* Open the loaded container and place it in a light cabinet or other suitable light device. The substance being examined should be exposed to light of 4500 lx ± 500 lx for 10 days and sampling at the fifth and the tenth day and examine the specified items for stability testing. Any changes in appearance of the substance should be noticed.

As to the light emitting device, It is recommended to use the device of the tunable exposure box. A light cabinet may also be used, in which several daylight lamps are placed to achieve the defined exposure, and the height of the sample platform may be adjusted. An aspirator is installed at the upper part of the cabinet to eliminate the heat possibly produced. An illuminometer is fixed on the cabinet to monitor the illumination of the cabinet at any moment. The light cabinet should not be interfered by natural light and keep the illumination intensity constant. Mote should be prevented in light cabinet.

According to the chemical, physical and microbiological properties of the drug, experiment can be designed when necessary for exploring the affect of pH, oxygen and other factors on stability of the drug, and analytical method of related substances should be developed. For innovative or new drugs, it is necessary to study the properties of their decomposition products.

2. *Accelerated testing* This testing is carried out under extraordinary conditions. The purpose is to study and predict the drug stability by accelerating the chemical or physical change of the drug to provide the necessary data for evaluation, manufacturing, transportation and storage of drug. Three batches of samples, with the package as same as the market package, are required for accelerated testing, being placed at 40°C ± 2°C/75% ± 5% RH for 6 months. The equipment must be capable of controlling the temperature within a range of ± 2°C and relative humidity of ± 5% RH and monitoring the actual temperature and humidity. The drug substance should be examined respectively at the first, second, third and sixth month during the testing periods according to the specific items for stability testing. If the examined substance does not conform to the quality standard in 6 months duration under conditions of accelerated testing at 40°C ± 2°C/75% ± 5% RH, additional testing at an intermediate condition, such as 30°C ± 2°C/65% ± 5% RH (saturated solution of NaCrO₄ may be used, the relative humidity is 64.8%-61.5% at 30°C), should be conducted for six months. It is recommended that a water-separating type of electric heating constant temperature culture box (20-60°C) be used for the accelerated testing. A dessicator containing a saturated salt solution with a definite relative humidity is put at the lower part of the box, the temperature should be even controllable as required and suitable for long-term use. A constant humidity and temperature box or other suitable device can also be used. For temperature sensitive or less stable drug substance, suppose to be stored only in a refrigerator (4-8°C), the six months accelerated testing may be carried out at 25°C ± 2°C/60% ± 5% RH.

3. *Long-term testing* Long-term testing is carried out under the conditions close to the actual storage conditions for the drug. The purpose is to provide data for the shelf life of the drug. Three batches of drug substance, with the package as same as market package are placed for 12 months under the defined long-term conditions (25°C ± 2°C/60% ± 10% RH). The stability testing on specified items will be carried out at

the 0, 3rd, 6th, 9th, 12th month. Thereafter, the examinations at the 18th, 24th and 36th month are still required. Shelf life of the drug is fixed by comparing the results at different duration with those at 0 month. Statistical analysis is generally conducted using 95% confidence limit because of the variation of the experimental data. If the variation of the statistical analytical results of the 3 batches is small, the average is taken as the shelf life, if the variation is significant, the value obtained in shortest duration is taken as the shelf life. If the variation of the results of stability testing is so small, the drug is taken to be stable, then the statistical analysis can be omitted.

For the drug substance less stable on temperature, long-term testing may be carried out at $6^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 12 months according to the above described requirements. The examination should be continued after 12 months. Shelf life of the drug stored at low temperature should be formulated based on the results of stability testing.

The condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ for long-term stability testing is adopted on the basis of the International climatic zone (see table).

Mean climatic conditions: calculated data and derived storage conditions¹

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	$^{\circ}\text{C}^2$	$^{\circ}\text{C}_{\text{MKT}}^3$	%RH ⁴	$^{\circ}\text{C}$	%RH
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	70

¹ Based on: Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. *DN9 development and industrial pharmacy*, 1993, 19: 27952830.

² Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19°C were set equal to 19°C .

³ MKT=mean kinetic temperature (see p. 198).

⁴ RH=relative humidity.

The United Kingdom, North Europe, Canada and Russia are in the region of temperate zone, The United States of America, Japan and West Europe (Portugal-Greece) are in the region of subtemperate zone. Iran, Iraq and Sudan are in the region of dry and hot zone. Brazil, Ghana, Indonesia, Nicaragua and Philippine are in the region of humid and hot zone. The long-term testing condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ RH is adopted because China is mostly in the region of subtemperate zone, which is basically consistent with that adopted by ICH.

The drug substance for accelerated testing and long-term testing should be packaged with simulated small barrel, but the material and packaging conditions should be similar with those of the big barrel.

Drug Preparation The stability studies for the drug preparation should be based on the knowledge of stability of the drug substance, especially the influence of temperature, humidity and light on the drug substance stability. During the process of formula optimization and technical designation, some necessary affecting factors testing should be carried out, and the packaging conditions should also be investigated to conduct the following testings:

1. **Accelerated stability testing** This testing is carried out

under exaggerated storage conditions. The purpose is to predict stability of the drug preparation by accelerating the chemical or physical change of drug preparation and provide the necessary data for evaluation, manufacturing, transportation and storage of the drug. Three batches of samples, with the package as same as market package, should be placed under the conditions of accelerated testing at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH for 6 months. The equipment must be capable of controlling temperature within a range of $\pm 2^{\circ}\text{C}$ and relative humidity of $\pm 5\%$ RH and monitoring the actual temperature and humidity during storage. The preparation should be examined respectively at the first, second, third, sixth month during the testing periods according to the specified items for stability testing. If the examined preparation does not conform to the quality standard during 6 months under above mentioned conditions, additional testing at an intermediate condition, such as $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\%$ RH, should be conducted for six months. Relative humidity is not required for Solutions, Suspensions, Creams and Injections. The equipment used is the same as those used for drug substance. For temperature sensitive or less stable drug preparation, suppose to be stored in a refrigerator ($4-8^{\circ}\text{C}$), the six months accelerated testing may be carried out at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ RH.

It is appropriate that the accelerated testing is directly carried out at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\%$ RH for Creams, Suspensions, Ointments, Eye ointments, Suppositories, Aerosols, Effervescent tablets and Effervescent granules, other requirements are the same as those described above.

For the drug preparations in semi-permeable container, such as Solutions in plastic bag, Eye drops or Nasal drops in plastic bottle, etc., the accelerated testing should be carried out at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/20\% \pm 2\%$ RH (saturated solution of $\text{CH}_3\text{COOK} \cdot 1 \frac{1}{2} \text{H}_2\text{O}$ may be used).

2. **Long-term stability testing** Long-term stability testing is carried out under the condition close to the actual drug storage conditions. The purpose is to provide data for the drug shelf life. Three batches of drug preparation with package as same as the market package are placed for 12 months under the defined conditions long-term stability testing at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 10\%$ RH. The stability testing on the specified items will be carried out at the 0, 3rd, 6th, 9th, 12th month. Thereafter the examinations at the 18th, 24th and 36th month are still required. The drug shelf life is fixed by comparing the results at different time duration with those at 0 month. Statistical analysis is generally conducted using 95% confidence limit because of the variation of the experimental data. If the variation of the statistical analytical results of the three batches is small, the average is taken as the shelf life, if the variation is significant, the shortest time duration is taken as the drug shelf life. Statistical analysis can be omitted for stable drug. For the temperature sensitive or less stable drug preparation, long-term testing may be carried out at $6^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 12 months and the preparation should be examined according to the time requirement described above. The shelf life of the drug stored at low temperature should be formulated based on the results of the stability testing. For some drug preparation, stability should be investigated in the process of use.

Important items of drug stability testing The major items are shown in the following table. The items of the various preparation types unlisted in this table may be determined according to the requirements for the correlated preparations.

Tab. The important items of stability testing for new drug substance and preparation

Type of preparation	Emphatic items for drug stability
Drug substance	Appearance, melting point, content, related substances, hygroscopic and other items selected according to monograph
Tablets	Appearance, content, related substances, disintegration time or dissolution or drug release
Capsules	Appearance, content, related substances, disintegration time or dissolution or drug release, water content, precipitate on the content of soft capsules
Injections	Appearance, content, pH, visible particles, related substances, sterility should be inspected
Suppositories	Appearance, content, softening time and related substances
Ointments	Appearance, homogeneity, particle size and related substances
Creams	Appearance, homogeneity, particle size, related substances and demixing
Pastes	Appearance, homogeneity, particle size and related substances
Gels	Appearance, homogeneity, particle size, related substances, demixing on emulsion
Ophthalmic preparations	Appearance clarity, visible particles, content, pH, and related substances for solutions Appearance, content, pH, related substances, particles size and redispersibility for suspensions Appearance, clarity, content, pH, related substances and sterility for eye lotions Appearance, clarity, content, pH, related substances, particles size and sterility for eye pills
Pills	Appearance, content, related substances and disintegration
Syrups	Appearance, content, clarity, relative density, related substances and pH
Oral solutions	Appearance, content, clarity and related substances
Oral creams	Appearance, content, demixing and related substances
Oral suspensions	Appearance, content, ratio of settling volume, related substances and redispersibility
Powders	Appearance, Content, particle size, related substances and uniformity of appearance
Inhale aerosols	Leakage rate, dose in each bottle, related substance, number of deliveries of each bottle, dose in each delivery and particle size distribution.
Powders for Inhalation	Emptying rate, number of deliveries of each bottle, dose in each inhale, related substances and particle size distribution
Sprays	Number of deliveries in each bottle, volume in each delivery, dose in each inhale, related substances and droplet size distribution
Granules	Appearance, content, particle size, related substances
Patches(transdermal patches)	Appearance, content, related substance, release rate and adhesion
Rinsing agents, lotions, enemas	Appearance, content, related substance, demixing(emulsion type), dispersibility(suspension type), sterile for rinsing agents
Liniment, Paints	Appearance, content, related substance, demixing(emulsion type), dispersibility(suspension type) filming for film paints
Ear preparation	Appearance, content, related substances. For Ear powders, sprays and semi-solid preparations, selection of items is base on requirements of the dosage form respectively.
Nasal preparation	Appearance, pH, content, related substances. For nasal powders, sprays and semi-solid preparations, selection of items is based on the requirements of the dosage form respectively.

Note: The variation of number and quantity of related substances including decomposition products and other products produced by other factors should be stated in the item of related substances. If possible, it should be stated that which related substance is the intermediate of the drug substance or decomposition product.

XX D Guidelines for Sustained, Controlled and Delayed Release Preparations

Comparing to ordinary preparations, sustained and controlled release preparations have longer therapeutic effect, lower adverse effects and lower dosing frequency. According to the requirements of the design of the preparations, drugs in these preparations can release in vivo slowly, and drug plasma concentrations show less peak-valley fluctuation, thus they can avoid adverse effects caused by extra amount of drugs beyond the therapeutic range (therapeutic window) and maintain the effective concentration in the therapeutic

range. Sustained and controlled release preparations also include ocular, nasal, ear, vaginal, rectal, oral cavity or dental, transdermal or subdermal, intramuscular and subdermal implant preparations, which can lag the release and absorption of drugs and avoid the "first pass effect" of *portahaptic* system. Delayed release preparations are those which do not release drug rapidly after administration, such as intestinal-specific drug delivery systems or colon-specific drug delivery systems which can avoid deactivation in stomach or stimulation of drugs to stomach. Delayed release preparations also include pulsatile release systems which burst release their drugs under certain conditions.

Release theories of sustained, controlled and delayed release preparations mainly include controlling dissolution, diffusion, *erosion* or a combination of dissolution and diffusion, sometimes also include osmotically controlled and ion-exchange mechanism. Releasing processes can be fitted using different equations,