STABILITY

Primary stability studies are intended to show that the active substance will remain within specification during the retest period if stored under recommended storage conditions.

1.1.1.iv Selection of Batches

Stability information from accelerated and long-term testing is to be provided on at least three batches. The long-term testing should cover a minimum of 12 months duration on at least three batches at the time of submission of the application for registration.

The batches manufactured to a minimum of pilot plant scale should be by the same synthesis route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of active substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale.

In the event of more than one manufacturer being used it must be confirmed that the same method of synthesis is used or extensive comparative data submitted including all aspects of quality, safety and efficacy.

Supporting information may be provided using stability data on batches of active substance made on a laboratory scale.

The first three production batches of active substance manufactured post approval, if not submitted in the original application for registration, should be placed on long-term stability studies using the same stability protocol as in the approved application for registration.

1.1.1.v Test Procedure and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability-indicating testing methods must be applied. The need for the extent of replication will depend on the results of validation studies.

1.1.1.vi Specifications

Limits of acceptability should be derived from the profile of the material as used in the preclinical and clinical batches. It will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials.

1.1.1.vii Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature sensitive active substances should be stored under an alternative, lower temperature condition which will then become the designated long-term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15 °C above this designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature). The designated long-term testing conditions will be reflected in the labelling and retest date.

STABILITY

	Conditions	Minimum time period at submission
Long-term testing	25 +- 2 °C/60 +- 5%RH	12 months
Accelerated	40 +- 2 °C/75 +- 5%RH	6 months

Where "significant change" occurs during six months storage under conditions of accelerated testing at 40 °C +- 2 °C/75%RH +- 5%, additional testing at an intermediate condition (such as 30 ° C +- 2 ° C/65% +- 5%RH) should be conducted for active substances to be used in dosage forms tested long term at 25 °C/60%RH and this information included in the application for registration. The initial application should include minimum of 6 months' data from a 12month study.

STABILITY

"Significant change" at 40 °C/75%RH or 30 °C/60%RH, is defined as failure to meet the specification.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods, and the further accumulated data can be submitted to the Council during the assessment period of the application. The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as may occur during shipping.

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

1.1.1.viii Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the active substance. Testing under the defined long-term conditions will normally be every three months over the first year, every six months over the second year and then annually.

1.1.1.ix Packaging/Containers

The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution.

1.1.1.x Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the active substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics), a retest period applicable to all future batches of the bulk active substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally

unnecessary to go through the formal statistical analysis but merely to provide a full justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend the retest period at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should cover not only the assay but the levels of degradation products and other appropriate attributes.

When degradation products are identified in significant amounts or suspected of toxicity, a concerned effort has to be made to collect the following additional information about the substance concerned:

- chemical structure
- cross-reference to any available information about biological effect and significance at the concentrations likely to be encountered
- procedure for isolation and purification
- mechanism of formation, including order of reaction
- physical and chemical properties
- specifications and directions for testing their presence at the levels of concentrations expected to be present, and
- indication of pharmacological activity, or inactivity or toxicity profile.

Where the route of degradation is not known, suitable screening chromatographic or other tests may be required.

Official compendia or other tests designed to identify impurities in the active substance used in the formulation may not necessarily be suitable for investigation into degradation products.

When it has been considered necessary to perform toxicity studies these results should be presented.

Consideration should be given to the stereo-chemical and polymorphic integrity of active substances.

Stability information gained should enable the applicant to institute a routine system whereby re-analysis to validate the conformance to specification of the active substance is done in order that the stability of the dosage form concerned is assured.

1.1.1.xi Statements/Labelling

A storage temperature should be based on the stability evaluation of the active substance. Where applicable, specific requirements should be stated, particularly for active substances that cannot tolerate freezing. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

STABILITY

A retest period should be derived from the stability information.

1.1.2 Well-known Chemical Entities (established active substances)

Literature data on decomposition process and degradability are generally available and must be included in the submission.

If degradation pathways/products are unknown, references to support such conclusions must be included or experimental data submitted. Reference to pharmacopoeias will not satisfy this requirement.

1.2 DOSAGE FORMS

1.2.1 Products containing New Chemical Entities

1.2.1.i General

The design of the stability program for the finished product should be based on the knowledge of the behaviour and properties of the active substance and the experience gained from clinical trial formulation studies and from stability studies on the active substance. The likely changes on storage and the rationale for the selection of product variables to include in the testing program should be stated.

1.2.1.ii Selection of Batches

Stability information from accelerated and long-term testing is to be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g., 25 000 to 50 000 tablets or capsules for solid oral dosage forms).

The long-term testing should cover at least 12 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large- scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied to release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of active substance.

Where an application includes different sources of active substances that are not physically and/or chemically equivalent and/or where the difference in physical and/or chemical specifications may adversely affect the stability of the product, stability studies should be performed on the final product manufactured from each active substance.

Data on laboratory scale batches is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information, provided that the difference in the formulations is clearly stated. The first three production batches manufactured post approval, if not submitted in the original application for registration should be