ASSESSMENT & MONITORING OF STABILITY

Stability

Characteristic of a reference material, when stored under specified conditions, to maintain a specified property value within specified limits for a specified period of time

- ✓ Long term stability – Stability under specified storage conditions
- ✓ Short term term stability – Stability under specified transport conditions.

Long term stability

Stability of a reference material property <u>over an extended period of time</u>

- ✓ At the shelves of the RMP
- ✓ At the specified storage conditions

Short term stability

Stability of a reference material (RM) property for the time period and conditions encountered in transportation to the user of the RM

Transportation stability has often been referred to as "short term stability".

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Life time (of an RM)

Time interval during which RM properties retain their assigned values within their associated uncertainties

The lifetime is often determined retrospectively, i.e. after RM properties no longer retain assigned values or attributes

Time interval during which the RM can be used

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Period of validity (of a RM)

Time interval during which the producer of the RM warrants its stability

- ✓ The period of validity may be expressed as a specific date or an otherwise defined period of time.
- ✓ The period of validity is designed to be within the lifetime of an RM.

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Assessment & monitoring of Stability

8.1 PREAMBLE

The value of each property can change over time for a variety of reasons, to different degrees, and at different rates depending on the conditions.

Three sets of conditions are particularly important:

- ✓ conditions during long-term storage at the RM producer's facilities,
- ✓ conditions during transport to the user's premises, and
- ✓ the specified conditions of storage and use at the user's premises.

8.1 PREAMBLE

The form and rate of change can differ considerably for different materials. Some change little or not at all under a wide range of conditions. Some change rapidly under ambient conditions and require low temperature storage.

The form of degradation can differ: some materials change almost linearly over long periods; some can undergo autocatalytic or less predictable rapid change after a period of stability.

Some can change rapidly during an initial period after processing and then remain stable over long periods.

8.1 PREAMBLE

These very different patterns of change, under different conditions, can be hard to predict even after extended experimental study.

There is, therefore, always some risk that the value of one or more properties will change unexpectedly during the life of a reference material.

RM producer is expected to manage material processing, storage, packaging, transport conditions, post-certification monitoring and advice to end users so that the risk of unexpected change is as small as reasonably possible.

8.1 PREAMBLE

RMP should do the following (as per ISO 17034:2016) to reduce the risk of unexpected change is as small as reasonably possible:

a) Assess the stability of all relevant properties of an RM under proposed storage conditions and choose pre-treatment, packaging and storage conditions accordingly;

b) assess, the stability of all relevant properties of an RM under planned conditions of transport, and choose transport conditions to maintain stability during transport;

c) establish any necessary advice on storage and use of the material to maintain stability at the user's premises;

8.1 PREAMBLE

d) select a scheme for monitoring the stability of materials held in long-term storage that permits prompt detection of change, taking into account the possible rate of change;

e) where the stability of a certified value cannot be ensured, make due allowance in the stated uncertainty for possible change in the value prior to use or, where the change with time can be predicted, provide a means of correcting the certified value and its uncertainty for expected change over time;

f) where repeated sampling from an RM unit, or repeated use of an entire RM unit, is permitted by the instructions for use, assess the possible effects on the stability of the material and take appropriate action.

8.1 PREAMBLE

RMP should select a combination of pre-treatment, packaging, storage, transport conditions and a monitoring scheme that lead to a reasonable expectation of negligible change over time.

Any means of correcting assigned values for predicted change over time will, for certified values, additionally require the estimation of the uncertainty associated with the corrected value

In practice, the only reliable way of estimating change over extended periods at a given set of conditions is to observe the material over the complete period of interest.

[i.e stability monitoring remains essential for any material intended to remain available for extended periods]

8.2 ASSESSMENT OF STABILITY

RMP should assess the stability of all RMs for both

- ✓ Certified value, and,
- ✓ Uncertainty of certified value (in case of CRM)

TYPES OF STABILITY:

— the long-term stability of the material (i.e. the stability of the material during the period of validity under specified storage conditions);

— the stability under reasonably expected conditions of transport (“transportation stability”), also called as short-term stability.

RMP should assess both LTS and STS of each property of interest prior to distribution of the material to users,

8.2 ASSESSMENT OF STABILITY

Stability assessment (LTS & STS) should be conducted to assess instability under more extreme conditions than those expected on the basis of planned storage and transport conditions.

8.2 ASSESSMENT OF STABILITY

Stability assessment should consider potential effects of re-use or repeated sub-sampling (including, for example, the effects of reopening, re-freezing or humidity) when this is permitted under stated conditions for use.

Need for experimental study of stability:

- ✓ RMP has little or no prior information on stability under the planned storage and/or transport conditions,
- ✓ where the effects of permitted re-sampling or re-use are not known,

Experimental studies are not necessary if the RMP has prior information on stability from closely similar materials held for an extended period under the same planned storage conditions.

8.3 CLASSIFICATION OF STABILITY STUDIES

Stability studies can be classified into

— classical and isochronous studies, according to the conditions of measurement,

— real-time studies and accelerated studies, according to stability study duration and conditions, and,

— transportation and long-term stability studies, according to whether they are aimed at evaluating stability under transport conditions or long-term stability in storage.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification according to conditions of measurement -

Classical stability studies

Individual samples prepared at the same time (i.e. as a batch), under identical conditions, are measured as time elapses (e.g. one sample immediately, one after three months, the next one after six months, etc.).

This design, in which the measurements are carried out under intermediate conditions of measurement (sometimes called within-laboratory reproducibility conditions),

This can lead to a relatively high uncertainty when instability of the measurement system contributes significantly to the dispersion of the measurement results.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification according to conditions of measurement -

Isochronous stability studies

Isochronous designs use storage under reference conditions to allow RM units exposed to different degradation conditions to be measured in a short period of time, ideally under repeatability conditions.

Reference conditions are a set of conditions under which the properties of interest can be reliably expected to be stable, or can be a chosen baseline level.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification according to conditions of measurement -

Isochronous stability studies

The word "isochronous" emphasizes that the measurements are made at the same time, rather than distributed over the time span of the stability study, as is the case in the classical approach.

Isochronous stability study, in theory, leads to a smaller uncertainty than that of the classical study, depending on the difference between the repeatability and the (within-laboratory) reproducibility of the measurements.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification according to conditions of stability study duration and conditions -

Real-time stability studies

In a real time stability study, the stability of a material is studied under the storage or transport conditions that are intended for the RM. This means that one week/month/ year of the stability study gives information on the behaviour of the material over a one week/month/year period.

This type of study has the advantage that it does not require any assumptions about the effects of different conditions on the stability, because the conditions used in the experimental study are the same as those intended for use in transport or storage.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification according to conditions of stability study duration and conditions -

Accelerated stability studies

Multiple experiments are performed at conditions that are more extreme than the storage or transport conditions intended for the RM

The aim is at inducing more rapid degradation than would be experienced under the intended storage conditions.

The degradation rate at the conditions of interest is then estimated, for example, by regression analysis over the various experimental conditions. The most frequent example is testing at several temperatures and estimating a degradation rate.

8.3 CLASSIFICATION OF STABILITY STUDIES

Accelerated stability studies

Advantages :

- ✓ Reducing the total time required and
- ✓ increased confidence from the use of information from more extreme exposure conditions

Disadvantages:

The degradation mechanism or its rate-determining step can change with different conditions under study, particularly the temperature.

8.3 CLASSIFICATION OF STABILITY STUDIES

Accelerated stability studies

- ✓ Both real-time and accelerated studies can be organized as classical or as isochronous studies.
- ✓ The use of accelerated studies can provide confidence in stability for periods substantially longer than the study duration and is particularly useful where early availability of the material is required.
- ✓ Light, moisture and temperature are common examples of factors that can accelerate degradation.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification by study objectives - Long-term stability studies

These are conducted to assess stability under storage conditions specified for the lifetime of the product.

Real-time long-term studies typically last 12 months or more; Accelerated studies are typically shorter but include more extreme conditions.

If fewer data are available about the stability of a property value in a material, the more extensive the long-term stability and post-certification monitoring should be.

Where time-to-market for new materials is crucial, it is possible to limit the long-term stability study to less than 12 months and perform frequent monitoring to complement the limited data available before certification.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification by study objectives - Transportation or other short-term stability studies

This study should be carried out to gain information concerning the appropriate conditions for transport. The duration of and conditions included in a transportation stability study should reflect the duration and conditions reasonably expected in transporting a unit of the RM to the user's premises.

These conditions should include extreme temperatures that might reasonably occur during international transport for a period that is at least as long as that allowed for transport of the RM. For example, if the proposed transport time is restricted to 3 weeks, a short-term stability study of 3 to 4 weeks will suffice.

8.3 CLASSIFICATION OF STABILITY STUDIES

Classification by study objectives - Transportation or other short-term stability studies

Transportation stability studies are assumed to be designed primarily to check for significant change rather than to provide an accurate quantitative estimate of change.

8.4 General requirements for effective stability studies

To obtain reliable results in a stability study, it is important to

— select a representative subset of material,

— choose a suitable measurement procedure with sufficient precision and selectivity,

— make the measurements under suitable conditions following an appropriate experimental design, and

— conduct the statistical analysis using valid statistical methods.

8.4 General requirements for effective stability studies

Selection of units :

- ✓ Randomly from the set of packaged units
- ✓ selection of units from the outer regions of a large set of RM units – such as the top or side of a large container or storage area – can result in selection of material exposed to light or more extreme temperature variation

Suitable measurement procedure(s) for stability studies

Outcome of the study is meaningful only if the SD of measurement results over the study time scale, is sufficiently small. This requires:

- ✓ For isochronous studies - good repeatability,
- ✓ For classical design at a single storage condition- good intermediate precision.

8.4 General requirements for effective stability studies

Experimental design:

The preferred nature of replication depends on the principal sources of variation, as follows.

— Where the measurement repeatability is the principal source of variation, the number of replicated measurements on each unit and/or the number of units studied at each combination of point in time should be increased.

— Where RM heterogeneity (represented by the between-unit standard deviation s_{bb}) is an important source of variation, the number of units studied at each time/condition combination should be increased.

— Where measurement variation over time in a classical stability study is important, the number of points in time should be increased.

8.4 General requirements for effective stability studies

Experimental design:

Exposure times

in a stability study are not necessarily equally spaced.

Temp (ºC)	4	20	40	70
Exposure time (Months)	1,3,6,12, (24)	1,3,6,12, (24)	1,3,6	0.5,1

8.5 Evaluation of stability study results

8.5.1 General considerations for stability study data treatment

Data treatment of stability studies should take account of:

- ✓ particular study objective,
- ✓ the experimental design used, and
- ✓ the sources of variation that might affect the results.

(a) Study objective

The objective is either to

- ✓ test for any important change over time in storage or
- ✓ estimate the rate of change of property values over time.

8.5 Evaluation of stability study results

8.5.4 Accelerated stability studies with multiple exposure conditions:

If no change is observed in an accelerated study then it is not possible to fit a reliable predictive model.

It is therefore useful for subsequent mathematical modelling to include changes in the conditions of accelerated study such that appreciable change is observed at least at the extremes.

Example of a layout of an accelerated ageing study:

Temp (ºC)	80	120	140	250
Exposure time (months)	1,3,6,12, (24)	1,3,6,12, (24)	1,3,6	0.5,1

Exposure times in parentheses show sampling times for the first post-certification monitoring (see 8.10)

8.6 Action on finding of a significant trend in a stability study:

If a technically significant trend (see 8.5.2.6) is observed, one of the following approaches should be adopted:

a) the property value is not certified;

b) the period of validity of the certified value is decreased;

c) the expected extent of degradation over the intended period of validity is estimated, converted into a standard uncertainty and included with the uncertainty of the expected degradation, in the uncertainty of the assigned value;

d) the certified value and its uncertainty are given as a function of time, reflecting the estimated trend and its uncertainty;

e) a combination of two or more of b), c) and d).

8.7 Uncertainty evaluation from stability studies

(a) Where valid technical reasons demonstrate that the potential change over the period of validity of the certificate is negligible compared with the certified uncertainty (e.g. less than $u_{CRM}/3$), and this is supported by experience and observation, then the component of uncertainty due to long-term stability may be set to zero or omitted from the uncertainty in the certified value.

(b) In other circumstances, where stability data analysis produces estimated rates of change, usually derived as, or from, coefficients in a fitted model, it becomes possible to predict potential future change based on the model

(c) Where little prior information is available about the behaviour of the material over extended periods of time (that is, larger than the stability study duration), and the RM producer chooses to employ comparatively infrequent monitoring (e.g. yearly or less), it is prudent to estimate these uncertainties and, for certified reference materials, to include them in the uncertainty associated with the certified value(s).

8.7 Uncertainty evaluation from stability studies

8.7.2 Sources of uncertainty in predicted change over time

A stability study includes the following sources of measurement variation that contribute to uncertainty :

a) repeatability of measurement;

b) between-run variability of the measurement system;

c) between-unit heterogeneity (in batch characterization).

In isochronous designs run-to-run variability is only present where multiple measurement runs are necessary

Uncertainties associated with random variability during the study should be included in any estimate of the uncertainty associated with a predicted change over time.

8.7 Uncertainty evaluation from stability studies

8.7.2 Sources of uncertainty in predicted change over time

In addition, systematic effects are present, including (but not limited to):

— uncertainties in model coefficients arising from measurement of time, or measurement of response;

— uncertainty arising from the choice of model, for example an assumption of linear degradation rather than exponential change.

Contributions associated with systematic effects on the measurement of time and response are usually much smaller than those arising from random variation.

8.7 Uncertainty evaluation from stability studies

8.7.3 Estimation of stability uncertainties in the absence of significant trends

When there is technical justification for stability (see 8.7.1), it may be assumed that the material is stable and the uncertainty associated with stability (u_{lts}) may be set to zero + adopt a monitoring regime that can detect unexpected change promptly. The choice of initial monitoring point and subsequent intervals are discussed in 8.10.

Where there is no technical justification for stability that is supported by experience, and where the RM producer elects to use longer monitoring intervals, an uncertainty associated with possible long term instability, u_{lts} should be estimated and included in the uncertainty associated with any certified value

8.7 Uncertainty evaluation from stability studies

8.7.3 Estimation of stability uncertainties in the absence of significant trends

For a simple linear model applied to a classical stability study over several points in time, the uncertainty u_{lts} associated with the predicted change is given by

$$u_{lts} = s(b_1) \times (t_{m1} + t_{cert})$$

where $s(b_1)$ is the standard error for the estimated slope, calculated as in B.3,
t_{m1} is the time interval between value assignment and the initial stability monitoring point and
t_{cert} is the period of validity of a certificate issued during that time.

8.7 Uncertainty evaluation from stability studies

8.7.4 Evaluation of stability uncertainties in the case of known significant trends

Where there is a known statistically significant or technically significant trend the RM producer may, following 8.6,

- ✓ provide a time-dependent certified value or
- ✓ may provide a time independent certified value and increase the prediction uncertainty.

When a time-dependent value is provided:

(a) the function for the certified value should reflect the best estimate of the trend and

(b) the function for the uncertainty should reflect the uncertainty of the trend (or, if appropriate, a correction), taking into account the sources of uncertainty listed in 8.7.2.

8.7 Uncertainty evaluation from stability studies

8.7.4 Evaluation of stability uncertainties in the case of known significant trends

When a certified value is given independently of time:

RMP should increase the prediction uncertainty to allow for expected change.

A period of validity, usually (t_{m1} + t_{cert}) as in 8.7.3 is chosen and the extent of degradation over that time is estimated. This is converted into a standard uncertainty (e.g. using a rectangular distribution if one observes a linear trend) and this uncertainty is combined (using uncertainty propagation rules) with the uncertainty of the predicted change

8.8 Estimation of storage lifetime ("shelf life") from a stability study

Where it is possible to set an acceptable level of change due to lack of stability for a certified value, it is possible to estimate a storage lifetime within which the value is expected to remain acceptable for use.

Acceptable level of change should be < 1/3 EU

The principles are described in B.4.

NOTE: An acceptable level of change can be set from, for example, a specification limit.

8.9 Instructions for use related to management of stability

Where repeated sub-sampling is permitted, the instructions for use should include:

- ✓ any precautions for prevention of contamination
- ✓ for storage of already opened units of the RM, that are necessary to ensure that the remaining material remains fit for use and,
- ✓ for CRMs, that the stated uncertainty is not compromised.

If property values can be affected by repeated sub-sampling, for example, by evaporation or by repeated refreezing, this should be noted on the certificate.

8.10 STABILITY MONITORING

Monitoring of a material following release is an important part of the overall management of stability for RMs with long usable life.

If shelf life, rates of degradation or uncertainty due to long-term storage, are to be decided based on experience of stability from previous RM production, RMP should have evidence to support claims of stability.

In these cases, the monitoring tests should include a measurement made at the expiry date for previous batches.

Monitoring is not necessary where the expected lifetime is short compared with known degradation rates for the same or closely similar materials.

In most other cases, some monitoring is normally considered necessary and should be undertaken at least once over the lifetime of the material to confirm stability.

8.10.2 Choice of initial monitoring point and monitoring interval(s)

Monitoring plans where extensive prior information is available

Where there is sound, relevant information from stability studies and/or monitoring of closely similar materials, covering a period similar to (or longer than) the expected lifetime of the material in question, the RM producer may set an initial monitoring point and intervals that are

— similar to those used successfully on closely related materials, or

— based on the observed change over time for the previous materials.

In the latter case, intervals should be set so that reasonably expected change between monitoring points, based on prior information, is not more than one third of the uncertainty associated with certified values.

8.10.2 Choice of initial monitoring point and monitoring interval(s)

Monitoring plans where extensive prior information is NOT available

RM producer should set initial monitoring points based on the stability study results for the material in question, and in addition plan for comparatively frequent monitoring at least for the first three monitoring points

There are two basic strategies for choosing initial monitoring points:

a) predict possible change and set the initial monitoring point prior to any change that adversely affects end use;

b) use a simple multiple of the stability study duration.

In both cases, a) and b), intervals for subsequent monitoring points (that is, after the first three points) should be set following review of the results of measurement at the first three monitoring points.

8.10.2 Choice of initial monitoring point and monitoring interval(s)

Monitoring plans where extensive prior information is NOT available

(i) Use of a predicted change to set the initial monitoring point

A specified tolerance for the certified value(s) is required. (This can be based on considerations for intended use).

1) A two-sided confidence interval for the change in certified value is constructed for a series of times following value assignment

2) the earliest point at which one of these limits intersects the limits of the specified tolerance is determined, either graphically or numerically

This point, or a convenient earlier time, is taken as the first monitoring point. Details are given in B.4

8.10.2 Choice of initial monitoring point and monitoring interval(s)

Monitoring plans where extensive prior information is NOT available

For a CRM, such an interval is usually based on the expanded uncertainty.

For example, choosing a tolerance of one third of the expanded uncertainty gives a low risk of the certified value moving outside of the expanded uncertainty prior to the first monitoring point.

8.10.2 Choice of initial monitoring point and monitoring interval(s)

(ii) Use of a simple multiple of the stability study duration

a) This strategy is simple but can result in shorter intervals than strategy (i).

b) It is based on multiples of the long-term stability study duration t_{lts}.

The multiple used should be chosen to limit the risk of a change that might affect the end use before the first monitoring point.

An example of an application of strategy (b) is given below:

— Set the first monitoring point at the later of the (i) value assignment date plus t_{lts} and the (ii) date of the end of the long-term stability study plus t_{lts}.

— Set two subsequent monitoring points at intervals of 2 t_{lts} from the first.

8.10.3 Experimental approaches and evaluation for stability monitoring

(a) Classical monitoring design

- ✓ Monitoring often takes place using the classical design.
- ✓ This involves measurement of RM units in normal storage at planned points in time.
- ✓ The evaluation of the results involves (i) a comparison of each (mean) monitoring result with the certified value and, (ii) over time, a check for any significant trend in the observed value.
- ✓ Advantage: Simplicity;
- ✓ Disadvantage: The results can be adversely affected by long-term variations in the measurement process.

8.10.3 Experimental approaches and evaluation for stability monitoring

(b) Evaluation of stability monitoring results

The basic evaluation of a single stability monitoring experiment applied to a CRM relies on comparison of the new measured value with the certified value. This approach requires the standard uncertainties u_{mon} and u_{CRM} associated with x_{mon} and x_{CRM}, respectively, and an appropriate coverage factor k at a level of confidence of approximately 95 %. Using this method, if the condition

$$| x_{CRM} - x_{mon} | \leq \text{Square root of } (u^2_{CRM} + u^2_{mon}) \times k$$

is not met, then it should be concluded that there is evidence of instability.

8.10.3 Experimental approaches and evaluation for stability monitoring

(b) Evaluation of stability monitoring results

- ✓ Where previous monitoring results on the same value are available in addition to the certified value, a check for a trend in the values should be performed.
- ✓ A check for a trend in the values over two or more monitoring points (in addition to the certified value) may be performed using simple linear regression.
- ✓ "Weights" may be applied if the uncertainties at different points differ appreciably.
- ✓ Where the gradient is significant at the 95 % level of confidence, it should be concluded that there is evidence of a trend in the values.

8.10.3 Experimental approaches and evaluation for stability monitoring

(b) Evaluation of stability monitoring results

$|x_{CRM} - x_{mon}| \leq$ Square root of $(u^2_{CRM} + u^2_{mon})$ x k

Where (a) the above criterion is not met or where (b) there is evidence of a trend, this indicates significant degradation of the material and action should be taken. Possible modes of action can include:

— performing confirmatory studies (with or without temporary suspension of RM distribution);

— halting distribution and discarding the material;

— re-certification of the material.