Real-time and accelerated storage stability studies

Common deficiencies in **storage stability studies**:

- incorrect storage temperature
- duration too short to support proposed storage period
- not all tests performed
- not enough data points for key parameters.

1. Purpose

This implementation guidance document is intended to provide guidance on generating and using accelerated and real-time storage stability data to establish a point of reference for quality control testing, determine the potential change in product characteristics during storage and to support a proposed storage statement.

2. Background

The purpose of storage stability studies is to generate evidence of the effect of storage on the physical and chemical properties of the product. This information can then be used to substantiate recommended storage conditions and limitations in the duration of storage prior to the initiation of use of the product.

To demonstrate that the product can maintain its characteristics during storage, real-time storage data in the manufacturer-recommended conditions must be generated. In addition to real-time storage studies, accelerated storage stability data must be generated using samples stored under conditions meant to “age” or stress the products over a shorter period. Conditions for generating accelerated stability data usually involve storage temperatures higher than the proposed storage conditions.

The available data which characterizes how a product behaves during storage should be used to inform manufacturers of recommendations for storage conditions and storage periods.

2.1. Accelerated storage stability study

The study should be conducted in a manner relying on established methods (for example, CIPAC MT 46.4) for accelerated storage stability. The purpose of the study is to investigate the potential changes in the product characteristics after exposure to elevated temperatures as compared to the manufacturing release specifications.

This study, however, provides limited insight into how the product may change during real-time storage under recommended conditions.

2.2. Real-time storage stability study

Due to the amount of time required to generate sufficient stability data to support the assignment of a recommended storage period, this study should be started as soon as the formulation has been finalized and the manufacturing process has been developed to the point where only minor changes are likely to be subsequently required (see Selection of batches below).

Findings of the real-time storage data should be used to provide guidance to procurers and stakeholders on the expectations of product stability when stored as recommended.

3. Design of stability studies

3.1. Selection and number of batches

Stability data should be generated using samples from at least three primary batches of at least pilot scale (that is, not less than one tenth of the proposed maximum production batch scale). The three batches used in stability studies should be taken from those used for the Module 3 chemical and physical characterization studies and for the Module 5 efficacy studies.

A primary batch is a batch with the same formulation as that proposed for commercial use manufactured using essentially the same manufacturing process. (Some changes to equipment and process parameters may be required to ensure that the characteristics of the product remain consistent on scale-up from pilot to production scale. This would still be considered essentially the same process.)

If applicable, more than one batch of the active ingredient (AI) intermediates used in the final formulation process should be used in the manufacture of the finished product batches used in the stability studies. Batches of intermediates should be of at least pilot scale; however, use of laboratory-scale batches may be acceptable if justified by data comparing the physical and chemical characteristics of laboratory- and pilot-scale batches.

The batches used should be clearly identified by batch number in both the raw stability data and the stability study reports.

3.2. Packaging

Products to be used in stability studies should be packed in the container proposed for commercial manufacture.

3.3. Storage conditions and duration of storage

The products should be stored under temperature-controlled conditions.

The storage temperature for the real-time study should be the temperature in the proposed storage statement.

3.4. Tests to be performed and testing schedule

The accelerated and real-time stability studies should include, at minimum, tests for appearance/description, mean content for each AI/synergist and content of any relevant impurities (if applicable). Any additional tests included in the manufacturing release specifications should also be included in the stability studies if it is generally reasonable that the parameter tested could change during storage.

The test methods used should be the same as those referenced in the premarket data requirements.

The appropriate number of samples should be used to perform the parameter test to be able to assess the results for the parameter separately for each batch. For example, for the mean AI content parameter for the accelerated stability study, at least three samples (one from each batch used in the study) should be tested.

For the real-time stability study, samples should be taken at the intervals shown in Table 1. The tests to be performed at each sampling time are those marked with an X in the appropriate column. As the primary consideration in this study is the measurement of changes over time rather than measurements of intra- and inter-batch variability, parameters can be measured using less samples within one batch but with representation of at least three batches. For example, for the mean AI content parameter, at least three samples (one from each batch used in the study) should be tested at each sampling time, with a total of at least 18 samples required for the mean AI content parameter (1 sample per timepoint x 6 timepoints x 3 batches).

Table 1. Parameters to be tested and testing schedule for storage stability

Tests	Accelerated storage stability	Real-time storage stability (months)						
	Post-ageing	0	3	6	9	12	18	24
Appearance/description	x	x		x		x	x	x
Mean AI/synergist content	x	x	x	x	x	x	x	x
Content of impurities (if applicable)	x	x		x		x	x	x
Any other relevant property as per spatial emanators IG	x	x				x		x

* Depending on the product, manufacturers may choose to extend or shorten the real-time storage study to align with their intended storage stability claim. In such cases, timepoints may be added or removed.

4. Assessment of the results

Results for each parameter should be assessed separately for each batch.

There should be little or no change in appearance/description, mean AI/synergist content, content of any relevant impurities (if applicable) or any other relevant property as per spatial emanators IG. In this context, little or no change means that any differences are within the intra-batch variability observed in the physical/chemical characterization studies.

Mean AI/synergist content and impurity content (if applicable) results should be plotted and a linear trendline fitted. The nature of the loss of AI/synergist and/or increase of impurities should be considered in order to characterize the reasons for the observed changes. If a decrease of mean AI/synergist content below the nominal concentration established based on batches from which efficacy data were generated is observed, a justification for the continuity of expected performance must be included. Any storage stability claims based on the analysis of these results should be correlated to the tolerances established for the manufacturing release specifications.

5. Stability commitment

Where the dossier does not include real-time storage stability data covering the full proposed duration of storage, a post-prequalification commitment for the applicant to supply the full data at the conclusion of the study will apply. If, during the study, any out-of-specification results are observed or if the results for any parameter do not follow the trends in the submitted data (for example, if changes are observed in a parameter that was previously stable, or if the rate of an observed change accelerates) the applicant is required to inform PQT/VCP.

In conjunction with the requirement to retain samples from each production batch, manufacturers may generate additional data on storage stability to further corroborate the available information on storage stability of the product.

6. Related documents

- WHO PQT/VCP Implementation guidance – Manufacturing release specifications