STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

ICH GUIDELINE Q1A(R2)

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General Principles

- The purpose of stability testing is:
  - to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light
  - to establish:
    - re-test period for the drug substance or
    - shelf life for the drug product
  - To recommended storage conditions.

Aim of the guidelines

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products.

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Stress Testing

Stress testing (drug substance)

- Studies undertaken to elucidate the intrinsic stability of the drug substance.
- Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)

- Studies undertaken to assess the effect of severe conditions on the drug product.
- Such studies include photostability testing and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

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Stress Testing

- Stress testing of the drug substance can help to:
  1. establish the intrinsic stability of the molecule
  2. identify the likely degradation products
  3. establish the degradation pathways
  4. validate the stability indicating power of the analytical procedures used.
- The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

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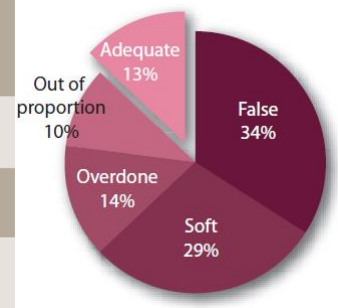
Table II: Type of degradation observed with a fixed set of fast and severe stress conditions.

Category	Explanation
Soft	No significant degradation and therefore no relevant degradation products observed
False	Fair amount of degradation (<15%), however no relevant degradation product(s) observed
Adequate	Fair amount of degradation (<15%) and at least one or all relevant degradation product(s) observed
Out of proportion	Between 15 and 100% degradation and at least one relevant degradation product observed
Overdone	Between 15 and 100% degradation, however, no relevant degradation products are observed



Klick et al. Pharm Technol. 2005 Feb;29(2):48-66.

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Stress Testing

- Stress testing is likely to be carried out on a single batch of the drug substance.
- It should evaluate :
  A. the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing),
  B. the effect of humidity (e.g., 75% RH or greater) where appropriate,
  C. Oxidation
  D. photolysis.
  E. the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

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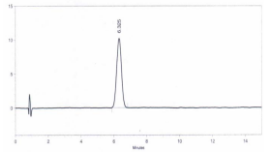
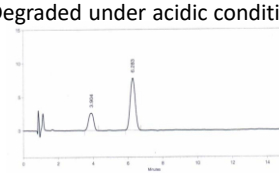
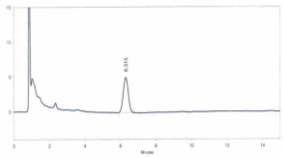
standard



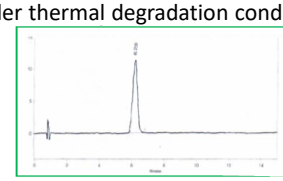
Degraded under acidic conditions



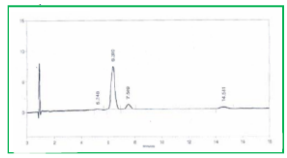
Degraded under basic conditions



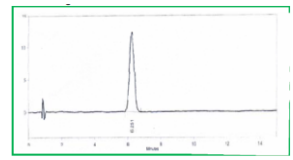
under thermal degradation conditions



Degraded under peroxide (H_2O_2) conditions



Exposed to direct sunlights



Chromatogram of Olopatadine HCl

Bhatt PD, Akhtar J. Int J. Pharmaeut. Sci. Rev. Res. 2011 Jul;2:153-8.

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Stress Testing

- Results from these studies will form an integral part of the information provided to regulatory authorities. Registration
- It may not be necessary to examine specifically for certain degradation products appearing in stress testing if it has been demonstrated that they are not formed under accelerated or long term storage conditions.

- **bracketing** is defined as "the design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design."
- **Matrixing** is "the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested."

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Selection of Batches

Pilot scale batch

- A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch.
- For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth (1/10) that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Production batch

- A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

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Storage Conditions: Drug substance

Primary batch

- A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively.
- A primary batch:
  - For a drug substance: should be at least a pilot scale batch.
  - For a drug product: two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps.
- However, a primary batch may be a production batch.

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Selection of Batches

	Drug substance	Drug product
Number of batches	3	3 (preferably from different batches of drug substance)
Scale	Minimum pilot	Two: at least pilot One: smaller scale, if justified
	method of manufacture simulates production scale	same formulation and package as proposed for marketing
		on each individual strength and container size unless bracketing or matrixing is applied
	same as or simulates the packaging proposed for storage and distribution	container closure system proposed for marketing (including any secondary packaging and container label)

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Specifications

	Drug substance	Drug product
Type	Release	Release and shelf life
	Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.	
	Validated stability-indicating analytical procedures should be applied.	
		Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness

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Testing Frequency

	Drug substance	Drug product
long term studies	long term studies 1st year: every 3 months 2nd year: every 6 months After the 2nd year: annually through the proposed re-test period/shelf life.	
accelerated storage condition	a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months),	

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Storage Conditions: Drug substance

- In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture.
- The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission.
- Testing should be continued for a period of time sufficient to cover the proposed re-test period.
- Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

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Storage Conditions : Drug substance

General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

****If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.**

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Storage Conditions : Drug substance

General case

- If long-term studies are conducted at 25 ± 2°C/60% ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.
- "Significant change" for a drug substance is defined as failure to meet its specification.
- Testing at the intermediate storage condition should include all tests, unless otherwise justified.
- The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

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Storage Conditions : Drug substance

Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

- If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.
- If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling.

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Storage Conditions : Drug substance

Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

- For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition.
- testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

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Storage Conditions : Drug substance

Drug substances intended for storage below -20°C

- Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

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Stability Commitment : Drug substance

- When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.
- Where the submission includes long term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

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Stability Commitment : Drug substance

Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, on long term stability studies through the proposed re-test period.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed re-test period.

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Storage Conditions: Drug product

- In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss.
- Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product (In-use stability).

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Storage Conditions : Drug product

- In-use stability testing should be performed on primary batches as part of the formal stability studies at initial and final time points.
- If full shelf life long term data will not be available before submission, in-use stability testing should be performed at 12 months or the last time point for which data will be available.
- In general, this testing need not be repeated on commitment batches.

➢WHO guidelines requires a minimum of two batches, at least pilot-scale batches, to be subjected to the test.

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Storage Conditions : Drug product

General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

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Storage Conditions : Drug product

General case

- If long-term studies are conducted at 25 ± 2°C/60% ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.
- The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

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Storage Conditions : Drug product

General case

"Significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;

   and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

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Storage Conditions : Drug product

Drug products packaged in impermeable containers

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

- Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent.

- Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

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Storage Conditions : Drug product

Drug products packaged in semi-permeable containers

Semi-permeable containers:

Containers that allow the passage of solvent, usually water, while preventing solute loss.

The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface.

In such cases, the concentration of drug (**assay**) may increase with time.

Examples of semi-permeable containers include:

- plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs)
- LDPE ampoules, bottles, and vials.

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Storage Conditions : Drug product

Drug products packaged in semi-permeable containers

- Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability.
- This evaluation can be carried out under conditions of low relative humidity (RH%).
- Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.
- Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

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Storage Conditions : Drug product

Drug products packaged in semi-permeable containers

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

**If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

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Storage Conditions : Drug product

Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

- If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available at the long term storage condition.
- If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling.

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Storage Conditions : Drug product

Drug products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

- For drug products intended for storage in a freezer, the proposed shelf life should be based on the real time data obtained at the long term storage condition.
- testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

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Storage Conditions : Drug product

Drug products intended for storage below -20°C

- Drug products intended for storage below -20°C should be treated on a case-by-case basis.

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Storage Conditions : Drug product

TABLE 2 Storage Conditions for Stability Evaluation of Drug Products

Stability Study Type	Stability Storage Conditions	Minimum Time Period Covered by Data at Submission (months)
Marketed Drug Product Intended for Room Temperature Storage Conditions		
Long term	25°C ± 2°C, 60% RH ± 5%	12
	RH or 30°C ± 2°C, 65% RH ± 5% RH	12
Intermediate	30°C ± 2°C, 65% RH ± 5% RH	6
Accelerated	40°C ± 2°C, 75% RH ± 5% RH	6
Marketed Drug Product Packaged in Semipermeable Containers		
Long term	25°C ± 2°C, 40% RH ± 5% RH or 30°C ± 2°C, 35% RH ± 5% RH	12
Intermediate	30°C ± 2°C, 65% RH ± 5% RH	6
Accelerated	40°C ± 2°C, no more than 25% RH	6
Marketed Drug Product Intended for Storage in Refrigerator		
Long term	5°C ± 3°C	12
Accelerated	25°C ± 2°C, 60% RH ± 5% RH	6
Marketed API Intended for Storage in Freezer		
Long term	−20°C ± 5°C	12

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Storage Conditions : Climatic Zones

- Climatic Zone I. *Temperate climate*, includes Canada, New Zealand, northern Europe, Russia, United Kingdom
- Climatic Zone II. *Subtropical* and Mediterranean climate, includes Japan, southern Europe, USA, southern Africa, parts of South America
- Climatic Zone III. *Hot and dry climate*, includes Argentina, Australia, Botswana, Middle East, northern Africa
- Climatic Zone IV. *Hot and humid climate*, includes Brazil, much of central Africa including Ghana and Nigeria, Indonesia, Nicaragua, the Philippines, Malaysia
  - IV-A: Hot and humid climate
  - IV-B: Hot and very humid climate

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Storage Conditions : Climatic Zones

Table 49.2 Long-term test conditions for the various climatic zones, as defined by the World Health Organization (2009)

Climatic zone	Definition	Long-term test conditions	
		Temperature (°C)	Relative humidity (% RH)
I	Temperate climate	21	45
II	Subtropical and Mediterranean climate	25	60
III	Hot and dry climate	30	35
IVA	Hot and humid climate	30	65
IVB	Hot and very humid climate	30	75

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Storage Conditions : Drug product

Climatic Zones III and IV: ICH Q1F

- ICH Q1 A (R2) adopted conditions corresponding to the ICH members (Zone I and II).
- For other countries in climatic Zone III/IV 30°C/65% RH was defined as the long-term storage condition in **ICH Q1F**.
- However, based on new calculations and discussions, some countries in Climatic Zone IV have expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than foreseen in ICH Q1F.
- As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30°C/75 % RH as the long-term storage conditions for hot and humid regions.

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Stability Commitment

- When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.
- Where the submission includes long term stability data on three production batches covering the proposed shelf life , a post approval commitment is considered unnecessary.

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Stability Commitment

Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed shelf life .
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed shelf life and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life .
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life.

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EVALUATION FOR STABILITY DATA

ICH GUIDELINE Q1E

General Principles

- The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.
- The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

General Principles

- it is important that the drug product be formulated with the intent to provide 100 percent of the labeled amount of the drug substance at the time of batch release.
- If assay at the time of release for stability batches is higher than 100 percent → the shelf life proposed in the application can be overestimated
- If the assay value of a batch is lower than 100 percent of label claim at the time of batch release, it might fall below the lower acceptance criterion before the end of the proposed shelf life.

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General Principles

- The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).
- The adequacy of the mass balance should be assessed.
- Factors that can cause an apparent lack of mass balance should be considered, including, for example:
  - the mechanisms of degradation
  - the stability-indicating capability of the analytical procedures
  - inherent variability of the analytical procedures.

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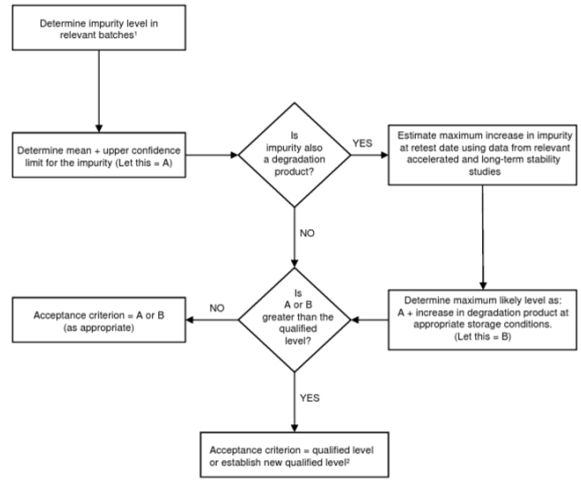
Data evaluation

➢**ICH GUIDELINE Q1E: Appendix A (Decision Tree page 8)**

DECISION TREE #1: ESTABLISHING ACCEPTANCE CRITERION
FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE



[1] Relevant batches are those from development, pilot and scale-up studies.
[2] Refer to ICH Guideline on Impurities in New Drug Substances

Definition: upper confidence limit = three times the standard deviation of batch analysis data

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Data evaluation: Statistical Approaches

- Various statistical tests are applied to ensure that the amount of drug remaining at the expiry date is above the lower acceptable limit.
- Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life.
- The relationship can be represented by a **linear or non-linear function** on an **arithmetic or logarithmic scale**. In some cases, a non-linear regression can better reflect the true relationship.

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Data evaluation: Statistical Approaches

- Various statistical tests are applied to ensure that the amount of drug remaining at the expiry date is above the lower acceptable limit.
- Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life.
- The relationship can be represented by a **linear or non-linear function** on an **arithmetic or logarithmic scale**. In some cases, a non-linear regression can better reflect the true relationship.

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Data evaluation: Statistical Approaches

- An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion.

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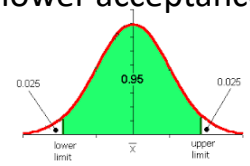
Data evaluation: Statistical Approaches

- For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion.
- For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the acceptance criterion.
- For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.



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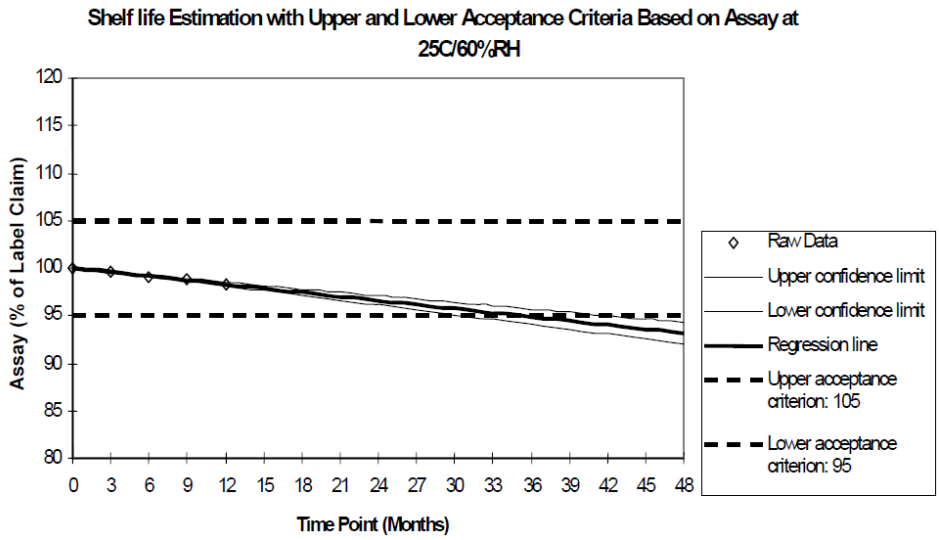
Data evaluation: Statistical Approaches



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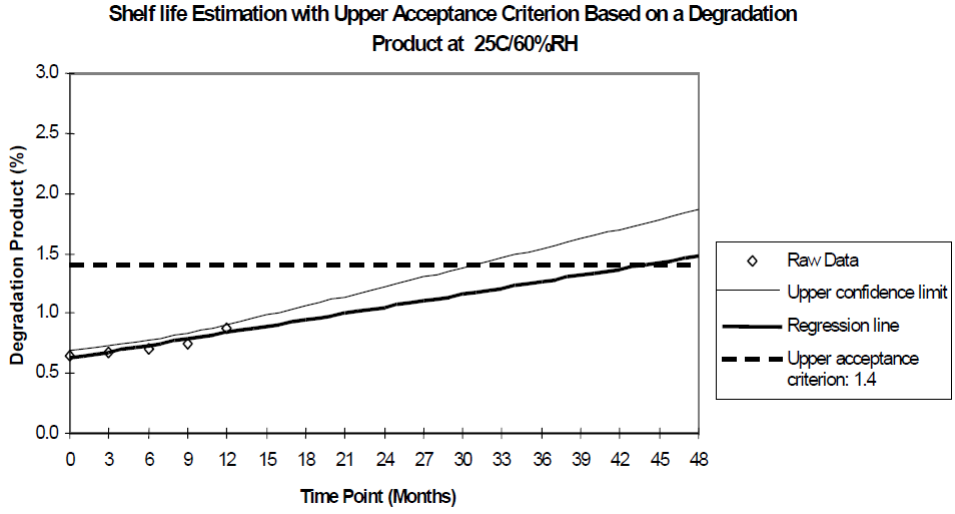
Data evaluation: Statistical Approaches



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Storage Conditions : Drug product

Summary of accelerated and intermediate storage conditions

Conditions	**Temperature**	**Humidity**	**Duration**
Accelerated /ambient	40 °C ± 2 °C	75% RH ± 5% RH	6 months
Accelerated /semipermeable container	40 °C ± 2 °C	NMT 25% RH	6 months
Accelerated /refrigerated	25 °C ± 2 °C	60% RH ± 5% RH	6 months
Intermediate	30 °C ± 2 °C	65% RH ± 5% RH	6 months

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In-Use Stability (WHO guidelines)

Aim:

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

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In-Use Stability (WHO guidelines)

Number and type of batches:

- A minimum of two batches, at least pilot-scale batches, should be subjected to the test.
- At least one of these batches should be chosen towards the end of its shelf-life.
- If such results are not available, one batch should be tested at the final point of the submitted stability studies.

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Table I: Investigated set of fixed stress conditions.

Temperature	Temperature and moisture	Light	Acid/base/ oxidative
30 min, 121 °C	1 week 70 °C, ambient	1 h xenon light (70–90 klx)	2 h 1 M HCl
	2 weeks 70°C, ambient	2 h xenon light (70–90 klx)	2 h NaOH
	1 week 70 °C, 100% RH	35 h UV light (~210 W h/m^2)	2 h 3% H_2O_2
	2 weeks 70 °C, 100% RH		

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