1.1

ICH Q1A(R2) Guideline

Stability Testing of New Drug Substances and Products

Comments for its application

ICH Q1(R2) Stability testing Guidelines: Stability Testing of New Drug Substances and Products

ICH Step 5
Recommended for Adoption 6 February 2003

Note for Guidance on Stability Testing:
Stability Testing of New drug Substances and Products

Revision of ICH Q1A:

- ❒ Section of stress testing of active substance from glossary to the main text
- ❒ Text on test procedures brought in line with Q6A
- ❒ Text on testing frequency amended for accelerated conditions
- ❒ Storage conditions described in more detail. Testing on low temperatures and aqueous liquid in semi-permeable containers
- ❒ Post -approval commitment described unambiguously
- ❒ Change 30°C ± 2°C/60% ± 5% to 30°C ± 2°C/65% ± 5%

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1. Introduction

1.1 Objective of the Guideline

- Revised version of ICH Q1A,
- defines stability data package or drug substance and drug product for registration application,
- within three regions of ICH, EC, Japan USA
- does not cover testing for registration in or export to other areas of the world
- Alternative approaches if scientifically reasons

1.2 Scope of the guideline

- Registration application for New Molecular Entity (NME) and associated Drug product.
- Not covered:
  - abbreviated or abridged applications,
  - variations,
  - clinical trial applications

1. Introduction

1.3 General Principles

- Purpose of stability testing is to provide evidence how quality varies with time under influence as
  - temperature
  - humidity
  - light,
- establish re-test period for drug substances
- establish shelf life for drug products
- recommend storage conditions
- Test conditions based on analysis of effects of climatic conditions in the three regions of the EC, Japan, USA
- mean kinetic temperature can be derived from climatic data
- world can thereby divided into four climatic zone I-IV
- This guideline addresses climatic zones I and II
- Stability information generated in one of the three regions is mutually acceptable to the other two provided:
  - information is consistent with this guideline,
  - labelling is in accord with national/ regional requirements.

The four Climatic Zones

Climatic Zone	Definition	Storage conditions
I	Temperate climate	21°C/ 45% r.h.
II	Subtropical and Mediterranean climate	25°C/60%r.h.
III	Hot, dry climate	30°C/35%r.h
IV	Hot, humid climate	30°C/70%r.h.

Criteria used to classify a site according to climatic zone

Criteria	Guide values for individual climatic zone			
	I	II	III	IV
Mean annual temperature measured in the open air	up to 15°C	> 15 – 22°C	> 22°C	> 22°C
Calculated mean annual Temperature (< 19°C)	up to 20.5°C	> 20.5 – 24°C	> 24	> 24
Mean annual Water vapour partial pressure	up to 11 mbar	> 11 – 18 mbar	up to 15 mbar	> 15 mbar

Measured and calculated climatic data for Atlanta

	January		May		July	
	7 a.m.	14 p.m.	7 a.m.	14 p. m.	7 a.m.	14 p. m.
Measured in the open	2.9°C/79%	11.1°C/59%	15.1°C/83%	26.1°C/54%	21.5°C/90%	30.6°C/64%
19°C used	19°C	19°C	19°C			
Arithmetic mean temperature	19°C/32%		22.6°C/59%		26.1°C/75%	
Mean kinetic temperature			23.2°C/58%		27.1°C/71%	

Mean kinetic temperature:

If a mean temperature is calculated and the difference between two temperatures is > 5°C the mean kinetic temperature should be calculated instead of the arithmetic mean temperature. This derives from the fact that the temperature dependency is not linear but logarithmic according to the Arrhenius equation. Haynes (7) has derived an equation based on the Arrhenius equation to calculate the T_{mkt}, the mean kinetic temperature:

$$T_{mkt} = \frac{\Delta E/R}{-\ln \frac{e^{-\Delta E/RT_1} + e^{-\Delta E/RT_2} + e^{-\Delta E/RT_n}}{n}}$$

ΔE: activation energy in kJ · mol^{-1} for which 83 kJ · · mol^{-1} can be set in (5).

Example:

20°C, 40°C: arithmetic mean temperature: · 30°C
mean kinetic temperature: · 34.4°C

Countries of climatic zones I and II

Europe:
EU, Belarus, Bulgaria, Estonia, Hungary, Latvia, Lithuania, Norway, Rumania, Russia, Switzerland, Ukraine

America:
USA, Argentina, Bolivia, Chile, Canada, Mexico, Peru, Uruguay

Africa:
Egypt, Algeria, Canary Islands, Libya, Morocco, Namibia, Rwanda, South Africa, Tunisia, Zambia, Zimbabwe

Asia:
Japan, Afghanistan, Armenia, Azerbaijan, China, Georgia, Iran, Israel, Kazakhstan, Kirghizia, Korea, Lebanon, Nepal, Syria, Tadzhikistan, Turkey, Turkmen, Uzbekistan,

Australia,
New Zealand.

1. Guidelines Drug Substance Drug Product

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2.1.2 Stress Testing

Stress Testing

- ❒ help identify likely degradation products
  but only those which are formed under accelerated and long term storage conditions
- ❒ establish degradation pathway
- ❒ establish intrinsic stability of molecule
- ❒ validate indicating power of analytical procedure
- ❒ depends on individual drug substance and type of drug product
- ❒ carried out on a single batch
- ❒ should include effect of
  - temperature e.g. 50°C, 60°C, 70°C etc.
  - humidity e.g. 75% or greater
  - oxidation
  - hydrolysis across a wide range of pH
  - photostability as described in ICH Q1B

Results from these studies form an integral part of information provided to regulatory authorities

2.1.3 Selection of Batches

Data from formal stability studies should be provided

- a least three primary batches
- manufactured to a minimum of pilot scale
- same synthetic route
- method of manufacture and procedure should simulate final process
- quality representative of quality to be made on production scale

Other supporting data can be provided

2.1.4 Container Closure System

❒ Container closure system same or simulates packaging proposed for storage and distribution

2.1.5 Specification

❒ **Specification:**
- list of tests,
- reference to analytical procedure,
- proposed acceptance criteria

❒ **Test Attributes**
- attributes that are susceptible to change during storage,
- influence quality, safety and/or efficacy
- Should cover physical, chemical, biological, microbiological attributes

❒ **Analytical procedures**
- validated stability indicating
- replication depending on results from validation studies

The following requirements for replication can be fixed:

RSD ≤ 1% single analysis
RSD > 1% 3fold analysis

The initial assay at time point 0 should be always analysed 3fold

2.1.6 Testing Frequency

- ❒ General: every 3 months first year, every 6 months second year, than annually through proposed re-test period: e.g. 0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months

- ❒ Accelerated storage condition: 0, 3, 6 months. Where expectation to approach significant change, increasing testing necessary: adding samples at final time point or forth time point in study design: 0, 3, 2 x 6 or 0, 1, 3, 6 months

2.1.7 Storage Conditions

Long term testing should cover a minimum of 12 months duration on at least three primary batches at time of submission and should be continued sufficient to cover the proposed re-test period.

- ❒ **General case**

Study	Storage condition	Study
Long term*	25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%	12 months
Intermediate**	30°C ± 2°C/65% ± 5%	6 months
Accelerated	40°C ± 2°C/75% ± 5%	6 months

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

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

2.1.7 Storage Conditions

- ❒ Drug substance intended for storage in a refrigerator

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

If significant change between 3 and 6 months at accelerated testing proposed re-test data based on real time data.

If significant change within 3 months discussion should address excursions outside label storage. Single batch shorter than 3 months with more frequent testing.

❒ **Drug substance intended for storage in a freezer**

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

Re-test period based on real time data at long term storage condition.
In absence of accelerated storage condition testing on a single batch at an elevated temperature e.g. 5°C ± 3°C to address short term excursions

2.1.8 Stability Commitment

❒ **Re-test period not covered**
When long term stability data do not cover proposed re-test period granted at time of approval commitment should be made to continue post approval to establish re-test period

❒ **Commitment not necessary**
Submission includes data on three production batches covering proposed re-test period

❒ **Commitment required**
- Submission includes data from 3 production batches, commitment to continue through proposed re-test period.
- Fewer than three production batches commitment
  continue with these studies through proposed re-test
  period and place additional production batches to a total of three on long term stability through proposed re-test period
- No Production batches commitment to place first
  three production batches on long term stability
  studies through proposed re-test period.

2.1.9 Evaluation

❒ **Re-test period**
Purpose of stability studies is to establish a re-test period applicable to all further batches of the drug substance manufactured under similar circumstances.
It is based on results of physical, chemical, biological and microbiological tests from three batches.

❒ **No formal statistical analyses**
The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these

circumstances normally unnecessary to go through the formal statistical analyses; Providing a justification for the omission should be sufficient.

❒ **Statistical evaluation**
Data on a quantitative attribute that changes with time: Determination of the time at which the 95% one sided confidence limit for the mean curve intersects the acceptance criterion etc,

2.1.9 Evaluation

❒ **Extrapolation**
Limited extrapolation of the real time data beyond the observed range to extend the re-test period can be undertaken at approval time, if justified.
Justification should be based on
- Knowledge on mechanism of degradation
- results of accelerated testing,
- goodness of fit of mathematical model
- existence of supporting data and batch size

2.1.11 Statements/Labelling

❒ **Storage Statement**
Storage statement established for labelling should be in accordance with national/regional requirements.
Statement based on stability evaluation

❒ **Re-test date**
Re-test date derived from stability information.
The re-test date should be displaced on the container label

2.2 Drug Product

❒ **2.2.1 General**
Design of the formal stability studies should be based on
- knowledge and properties of drug substance,
- experience gained from clinical formulation studies.

❒ **2.2.2 Photostability Testing**
One primary batch, standard conditions according to ICH Q1B

2.2.3 Selection of Batches

- ❒ Required are at least three primary batches.
  - Same formulation and in same container closure system as proposed for marketing.
  - Manufacturing process should simulate that applied to production batches.
  - Same quality and meeting specifications as that intended for marketing.
- ❒ Two of the three batches at least pilot scale third can be smaller
  - for solid oral dosage forms pilot scale is generally on tenth that of full production scale or
  - 100000 tablets or capsules, whichever is larger.
- ❒ Drug products should be manufactured by using different batches of the drug substance.
- ❒ Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.
- ❒ Other supporting data can be provided.

2.2.4 Container Closure System

- ❒ Container closure system proposed for marketing (if appropriate any secondary packaging and container label)
- ❒ Supporting information:
  - results of open storage of stress testing
  - studies in other packaging materials

2.2.5 Specification

- ❒ **Specification is a list of**
  - tests, test attributes
  - reference to analytical procedures
  - proposed acceptance criteria release and shelf life
- ❒ **Test attributes**
  - attributes susceptible to change during storage
  - may influence quality, safety and/or efficacy
  - should cover physical, chemical, biological, microbiological attributes.
- ❒ **Analytical procedures**
  - fully validated and stability indicating
  - Replication will depend on results of validation studies:
    Following requirements were fixed:
    RSD ≤ 1.5% single analysis
    RSD > 1.5% 3fold analysis
    Initial analysis generally 3fold

❒ **Acceptance Criteria**
- based on all available stability information
- differences between release and shelf life acceptance criteria justified
- difference for antimicrobial preservative content supported by validated correlation of chemical content and preservative effectiveness
- Single primary batch should be tested for antimicrobial preservative effectiveness at proposed shelf life

2.2.6 Testing Frequency

❒ **Long term studies**
- first year every three months. 0, 3, 6, 9, 12
- second year every six months: 12, 18, 24
- third year and longer annually: 24, 36, 48, 60

❒ **Accelerated studies**
- general minimum three time points: 0,3,6 months
- expectation of significant change increases testing adding samples at final time point or forth time point: 0, 3, 2x6 or 0, 1, 3, 6 months

❒ **Intermediate storage condition studies**
Minimum four time points, including initial and final e.g.: 0,6,9,12 months, at time of submission 0,6 months

❒ **Reduced design**
Matrixing or bracketing for reduction of testing frequency if justified

2.2.7 Storage conditions

Storage conditions and lengths of studies sufficient to cover storage shipment and subsequent use.
Stability testing of products after constitution or dilution should be conducted to provide information for labelling of *storage condition* and *in-use period.*
Primary batches initial and final time point, at least at 12 months.

❒ Long term testing should cover al least 12 months
❒ Should be continued to cover proposed shelf life
❒ Accelerated testing to evaluate short term excursions outside label storage condition

❒ **2.2.7.1 General case**

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

*It is up to the applicant, to decide whether long term stability is performed at 25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%.
** If 30°C ± 2°C/65% ± 5% is the long-term condition, there is no intermediate condition.

Testing at intermediate storage condition if significant change at accelerated testing

2.2.7 Storage Conditions

❒ **Significant change**

- A 5% change in assay from initial value,
- Any degradation product's exceeding its acceptance criterion,
- Failure to meet acceptance criteria for appearance, physical attributes, and functionality test.
  - Some changes as softening of suppositories, melting of creams are acceptable.
- Failure to meet acceptance criteria for dissolution for 12 units.

❒ **2.2.7.2 Drug products in impermeable container**
Studies can be conducted under any controlled or ambient humidity condition

❒ **2.2.7.3 Drug products in semi-permeable container**

- Evaluation for potential water loss for aqueous-based products in semi-permeable containers
- Evaluation under condition of low relative humidity

Study	Storage condition	Minimum time period at submission
Long term	25°C ± 2°C/40% ± 5% or 30°C ± 2°C/35%± 5%	12 months
Intermediate	30°C ± 2°C/35%± 5%	6 months
Accelerated	40°C ± 2°C/not more than 25%	6 months
Accelerated	40°C ± 2°C/75% ± 5%	6 months

*It is up to the applicant, to decide whether long term stability is performed at 25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%.
** If 30°C ± 2°C/65% ± 5% is the long-term condition, there is no intermediate condition

2.2.7 Storage Conditions

❒ A significant change in water loss alone during 6 months accelerated testing does not necessitate storage at inter-mediate condition, but no significant water loss at 25°C/40%.
❒ A significant change is a 5% water loss after 3 months accelerated testing
❒ For small containers (1 ml or less) more than 5% loss after 3 months may be appropriate

❒ **Alternative Testing**

- Storage under general storage conditions and calculate water loss by determining permeation coefficient or using calculated ratio of water loss.

Table with calculated ratio of water loss

Alternative relative Humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% r.h.	25% r.h	2.4
60% r.h.	40% r.h.	1.5
65% r.h	35% r.h.	1.9
75% r.h.	25% r.h.	3.0

2.2.7 Storage Conditions

❒ 2.2.7.4 Drug products intended for storage in a refrigerator

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

- If significant change between 3 and 6 months at 25°C/60% shelf life based on real time data
- If significant change within 3 months, discussion about short term excursions outside label storage.
- As possible support one batch shorter than 3 months and more frequent testing

❒ 2.2.7.5 Drug products intended storage in freezer

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

- Shelf life based on real time data
- testing on a single batch at 5°C for appropriate time period

2.2.8 Stability Commitment

❒ **Proposed shelf life not covered**

When long term stability data do not cover proposed shelf life granted at time of approval commitment should be made to continue post approval to establish the shelf life

❒ **Commitment not necessary**
Submission includes data on three production batches covering proposed shelf life

❒ **Commitment required**
- Submission includes data from 3 production batches, commitment to continue through proposed shelf life
- Fewer than three production batches commitment continue with these studies through proposed shelf life and place additional production batches to a total of three on long term and accelerated stability testing through proposed shelf life.
- No Production batches commitment to place first three production batches on long term and accelerated stability testing through proposed shelf life.

2.2.9 Evaluation

❒ **Stability information**
- Systematic approach in presentation and evaluation of stability information.
- Should include results from physical, chemical, biological and microbiological tests.

❒ **Purpose of stability studies**
Establish shelf life and storage instructions applicable for all further batches manufactured and packed under similar circumstances.

❒ **No formal statistical analyses**
Where data show so little degradation and so little variability that it is apparent from looking at the data, the requested shelf life will be grated without formal statistical analyses. But justification for omission

❒ **Formal statistical analyses**
For quantitative attributes which change with time determination of time at which the 95% one sided confidence limit for the mean curve intersects the acceptance criteria.
Data of batches can be combined if
- batch to batch variability is small
  - slope of regression line
  - zero time intercepts

❒ **Extrapolation**
Limited extrapolation can be undertaken at approval time with justification

2.2.10 Statements/Labelling

❒ **Storage Statement**
- Storage statement for labelling in accordance with national/regional requirements
- Based on the stability evaluation
- Direct link between label storage statement and demonstrated stability.
- Expiration date should be displayed on container label.

References

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