ICH GUIDELINES FOR STABILITY STUDIES

BY

O.PRIYANKA
M Pharm 1st yr.
ICH GUIDELINES FOR STABILITY STUDIES:

- Q1A(R2) - Stability Testing of New Drug Substances and Products
- Q1B - Stability Testing: Photostability Testing of New Drug Substances and Products
- Q1C - Stability Testing for New Dosage Forms
- Q1D - Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- Q1E - Evaluation of Stability Data
- Q1F - Stability Data Package for Registration Applications in Climatic Zones III and IV
ICH guideline Q1-A(stability studies)

- **OBJECTIVE OF THE GUIDELINE:**
  It defines stability of drug substance and drug product for registration of application of NCE or associated drug, within three regions of ICH i.e.; EU, Japan, USA.

**NOTE:** It does not cover testing for registration of drug substance or product intended for import or export to other areas of the world.
1. Purpose of stability testing is to provide evidence how quality varies with time under influence of
   - temperature
   - humidity
   - light

2. Establish re-test period for drug substances

   **RETEST PERIOD:** the period after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification, and thus suitable for use in manufacturing.

   A retest period should be proposed on the basis of stability results and may be extended to five years (e.g., Ethambutol 2HCl, or Isoniazid)

3. Establish shelf life for drug products

   **SHELF LIFE:** (EXPIRY DATE/EXPIRATION DATING PERIOD)
   The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product.

   The shelf-life is used to establish the expiry date of each batch.
4. recommends storage conditions
5. Gives Test conditions based on analysis of effects of climatic conditions in the three regions of the EU, Japan, USA.
6. Gives mean kinetic temperature which is derived from climatic data
7. divided world into four climatic zone I-IV
   - This guideline addresses climatic zones I and II
8. And the 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.
### CLIMATIC ZONES:

<table>
<thead>
<tr>
<th>CLIMATIC ZONE</th>
<th>DEFINITION</th>
<th>STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>TEMPERATE CLIMATE</td>
<td>21°C/45 % R.H</td>
</tr>
<tr>
<td>II</td>
<td>SUBTROPICAL AND MEDITERRANEAN CLIMATE</td>
<td>25°C/60 % R.H</td>
</tr>
<tr>
<td>III</td>
<td>HOT, DRY CLIMATE</td>
<td>30°C/35 % R.H</td>
</tr>
<tr>
<td>IV</td>
<td>HOT, HUMID CLIMATE</td>
<td>30°C / 70% R.H</td>
</tr>
</tbody>
</table>
## STEPS IN STABILITY TESTING OF DRUG SUBSTANCE OR PRODUCT

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress Testing</td>
<td>Photostability Testing</td>
</tr>
<tr>
<td>Selection of Batches</td>
<td>Selection of Batches</td>
</tr>
<tr>
<td>Container Closure System</td>
<td>Container Closure System</td>
</tr>
<tr>
<td>Specification</td>
<td>Specification</td>
</tr>
<tr>
<td>Testing frequency</td>
<td>Testing frequency</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Storage Conditions</td>
</tr>
<tr>
<td>Stability Commitment</td>
<td>Stability Commitment</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Evaluation</td>
</tr>
<tr>
<td>Statements/Labelling</td>
<td>Statements/Labelling</td>
</tr>
</tbody>
</table>

O.priyanka, department of pharmaceutics, GPRCP

9/10/2012
What is the use of stress testing:

- To **validate** the stability indicating power of the analytical procedures.
- To **identify stability-affecting factors** such as ambient temperature, humidity and light and to select packing materials which protect the formulation against such effects.
- To **identify potential degradants** of the API and assess if they can be formed during manufacture or storage of the formulation.
- To **select manufacturing process** for particular drug substance.
<table>
<thead>
<tr>
<th>Test parameter</th>
<th>procedure</th>
<th>observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>A thin layer of the API is wetted with water and is kept at 80°C for 4 weeks in a Petri dish (open system) with sampling once a week</td>
<td>Assay:</td>
</tr>
<tr>
<td>Humidity</td>
<td>A thin layer of the API is wetted with water and kept at 40°C / 100% RH for 4 weeks in a Petri dish (open system) with sampling once a fortnight</td>
<td>“</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Oxygen is bubbled slowly through the oxygen-saturated aqueous solution/suspension (under constant mixing) of the API for 24 hours with sampling every eight (8) hours</td>
<td>“</td>
</tr>
</tbody>
</table>
ASSAY of certain compounds is difficult:

- Example: artesunate
- Reason: increase in concentration of API
- During stability studies of **Artesunate**, the assay results were increasing. The hydrolysis yields artemimol and succinic acid. The formation of succinic acid justifies the increase in assay. The assay method is „stability indicating” but not specific.
## STRESS TESTING: (forced degradation)

<table>
<thead>
<tr>
<th>Degradation factor</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal</td>
<td>$\geq 60 , ^\circ C$</td>
</tr>
<tr>
<td>Humidity</td>
<td>$\geq 75%$ RH</td>
</tr>
<tr>
<td>Acid</td>
<td>0.1N HCl</td>
</tr>
<tr>
<td>Base</td>
<td>0.1N NaOH</td>
</tr>
<tr>
<td>Oxidative</td>
<td>Oxygen gas, or 3$%$ H$_2$O$_2$</td>
</tr>
<tr>
<td>Photolytic</td>
<td>Metal halide, Hg, Xe lamp, or UV-B fluorescent</td>
</tr>
<tr>
<td>Metal ions (optional)</td>
<td>0.05M Fe$^{2+}$ or Cu$^{2+}$</td>
</tr>
</tbody>
</table>
STRESS STABILITY TESTING:

• An optimal degradation pattern generated during stress testing would show only those degradation products observed at the end of shelf life in regulatory stability studies and those that might appear if the API or formulation if not manufactured, handled or packed properly.

• Chromatograms thus obtained will be representative and not too complicated to evaluate, which may be the case if drastic conditions are applied and many second- and third-generation degradation products are formed.
## Stress stability testing - Nevirapine

<table>
<thead>
<tr>
<th>STRESS TYPE</th>
<th>CONDITIONS</th>
<th>ASSAY(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>25° C</td>
<td>99.8</td>
</tr>
<tr>
<td>36% HCl</td>
<td>80° C, 40 min.</td>
<td>72.0</td>
</tr>
<tr>
<td>5N NaOH</td>
<td>80° C, 2h 20’</td>
<td>98.6</td>
</tr>
<tr>
<td>30% w/w H₂O₂</td>
<td>80° C, 2h 20’</td>
<td>98.6</td>
</tr>
<tr>
<td>Heat</td>
<td>130° C, 49h</td>
<td>101.5</td>
</tr>
<tr>
<td>light</td>
<td>500W/m², 68h</td>
<td>101.7</td>
</tr>
<tr>
<td>Water</td>
<td>25° C, 92% RH, 91h</td>
<td>101.2</td>
</tr>
</tbody>
</table>
Selection of Batches

- Data from formal stability studies should be provided
- at least three primary batches are selected.
- From batches manufactured to a minimum of pilot scale
- from batches having same synthetic route
- From a batch where method of manufacture and procedure simulates final process.

- Other supporting data can be provided
Container Closure System

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

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

**Test Attributes**
- attributes that are susceptible to changed storage,
- influence quality, safety and/or efficacy
- Should cover physical, chemical, biological and 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
Testing Frequency

- **General**: every 3 months first year, every 6 months second year, then 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, 2x 6 or 0, 1, 3, 6 months
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:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term*</td>
<td>25°C ± 2°C/60% ± 5% or 30°C ± 2°C/65% ± 5%</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate**</td>
<td>30°C ± 2°C/65% ± 5%</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% ± 5%</td>
<td>6 months</td>
</tr>
</tbody>
</table>

**NOTE:**

*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.*
Drug substance intended for storage in a refrigerator

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>5°C ± 3°C</td>
<td>12 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25°C ± 2°C/60% ± 5%</td>
<td>6 months</td>
</tr>
</tbody>
</table>

If significant change between 3 and 6 months at accelerated testing propose 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>- 20 °C ± 5°C</td>
<td>12 months</td>
</tr>
</tbody>
</table>

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 address short term excursions.
Stability Commitment

- When Re-test period not covered or not mentioned
- 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.
- Not required for Submission which 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.
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.

1) **No formal statistical analyses needed for**
   The data may show so little degradation and so little variability 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.

2) **Statistical evaluation**
   For the Data that changes with time statistical evaluation is required.
Compliance alert:
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
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 displayed on the container label
Significant change of drug substance or product:

- A 5% change in assay from its initial value.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).
- As appropriate for the dosage form, e.g., failure to meet the acceptance criteria for dissolution for 12 dosage units.
Photostability testing: Q1-B

- A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:
  i) Tests on the active substance;
  ii) Tests on the exposed product outside of the immediate pack, and if necessary;
  iii) Tests on the product in the immediate pack; and if necessary;
  iv) Tests on the product in the marketing pack.
Light sources:

- D65/ID65 emission
- standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp.
- D65 is the internationally recognised standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation.
NEW DOSAGE FORMS-Q1 C

definition:
• A new dosage form is defined as a medicinal product which is a different pharmaceutical product type, but containing the same active substance as included in an existing product approved by the pertinent regulatory authority.

Include:
• products of a different route of administration (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same route of administration (e.g., capsule to tablet, solution to suspension).
• Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time may be acceptable with proper justification.
• e.g.,
6 months accelerated and 6 months long term data from ongoing studies may be acceptable in certain justified cases.
STABILITY TEST PARAMETERS FOR VARIOUS TYPES OF PRODUCTS

- Tablets – Appearance, colour, odour, assay, disintegration/dissolution, moisture and friability or hardness testing.
- Hard gelatin capsules - Appearance, colour, odour of contents, assay, disintegration/dissolution, moisture and microbial limits
- Soft gelatin capsules - Appearance, colour, odour of contents, assay, disintegration/dissolution, moisture, microbial limits, pH, leakage and pellicle formation.
- Emulsions – Appearance including phase separation, colour, odour, assay, pH, viscosity, preservative content, weight loss and microbial limits.
• Suppositories – Appearance, colour, assay, particle size, softening range, appearance, dissolution and microbial limits.

• Small volume parenteral: Drug injection – Appearance, colour, assay, ph, preservative, content, particulate matter, sterility and pyrogenicity.

• Large volume parenteral - Appearance, colour, assay, ph, preservative content, particulate matter, sterility and pyrogenicity

• Transdermals – Appearance, assay, leakage, microbial limit/sterility, peel and adhesive forces, drug release rate.
Q1D- Bracketing and Matrixing Designs for Stability Testing:

- **guideline** Recommends for application of bracketing and matrixing

**Applicability of Reduced Designs**
- Applicable to formal stability studies of most types of drug products
- Drug substances: matrixing limited, bracketing generally not applicable
- Whether bracketing or matrixing depends on circumstances
- Any reduced design should be justified.
- Type and level of justification depends on available supporting data.
- Careful consideration and scientific justification, if bracketing and matrixing in one design.
BRACKETING:

- Bracketing is the design of a stability schedule such that only the extremes of certain design factors are tested at all time points.
  - different strengths
  - different container size and/or fill
- Stability of intermediate levels represented by stability or tested extremes.
- Bracketing design not appropriate, if tested samples are not the extremes.
**DESIGN EXAMPLE:**

- Three strengths and three container sizes:

<table>
<thead>
<tr>
<th>Container size</th>
<th>Dosage strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg</td>
</tr>
<tr>
<td>15 ml</td>
<td>T</td>
</tr>
<tr>
<td>100 ml</td>
<td></td>
</tr>
<tr>
<td>500 ml</td>
<td>T</td>
</tr>
</tbody>
</table>

9/10/2012

O.priyanka, department of pharmaceutics, GPRCP
MATRIXING:

- Matrixing is the statistical design of a stability schedule.
- Each storage condition should be treated separately under its own matrixing design.
- At a given time point (other than the initial or final ones) not every batch on stability needs to be tested.
- Full testing must be performed at the maximum storage period at the time of submission.
Design example:

<table>
<thead>
<tr>
<th>Type</th>
<th>Storage period in months (time points)</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>A</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>B</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>
### Bracketing or matrixing?

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>Preferable procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predevelopment</td>
<td>bracketing</td>
</tr>
<tr>
<td>Clinical phases I-III</td>
<td>bracketing</td>
</tr>
<tr>
<td>Accelerated and long term testing with registration batches</td>
<td><strong>bracketing /matrixing</strong></td>
</tr>
<tr>
<td>On-going stability testing</td>
<td>matrixing</td>
</tr>
<tr>
<td>Follow-up stability testing</td>
<td>matrixing</td>
</tr>
</tbody>
</table>

**9/10/2012**

O.priyanka, department of pharmaceutics, GPRCP
Objectives of the Guideline:

- How to propose a retest period for drug substances and a shelf life for drug products in the registration application.
- When and how an extrapolation beyond available data can be considered.
- Q1F- Stability Data Package for Registration Applications in Climatic Zones III and IV

Objectives of the Guideline:

- Application of ICH Q1A(R) in countries of Climatic zones III and IV
References:

- [apps.who.int/prequal/trainingresources/pq.../stabilitystudies.ppt](http://apps.who.int/prequal/trainingresources/pq.../stabilitystudies.ppt)
- N K Jain Pharmaceutical Product Development
Thank You!

By O.priyanka
m pharm 1st year
department of pharmaceutics
GPRCP