Stability Studies:
Experience of assessing stability data provided by the applicants to the Prequalification Programme

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Focus of the presentation

- Purpose of stability
- Common deficiencies
- Requirements
- WHO Generic Guideline
- Conclusion
The purpose of stability testing is to provide evidence of how the quality of an Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Product (FPP) varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials.
Stability summary and conclusions

- The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

- It should also include: Stress testing, Accelerated, intermediate (if necessary) and long-term testing, Proposed storage statement and shelf-life.
Summary/ evaluation of stability data

- The information on the stability studies should include details such as:
  - storage conditions;
  - strength;
  - batch number, including the API batch number(s) and manufacturer(s);
  - batch size;
  - container closure system including orientation (e.g. erect, inverted, on-side) where applicable; and
  - completed (and proposed) test intervals.
Evaluation/ discussion of stability data

- **Common deficiency:**
  
  Failure to evaluate and discuss stability data and provide a conclusion. Trends and OOS results are not explained and discussed.

- **Requirement:**
  
  The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results and any trends that were observed.
Minimum long term and accelerated data

- **Common deficiency:**
  
  Failure to provide the minimum required stability data at the time of submission and to update the data as the assessment progresses.

- **Requirement:**
  
  The minimum data required at the time of submitting the dossier (in the general case):

<table>
<thead>
<tr>
<th>Storage temperature (°C)</th>
<th>Relative humidity (%)</th>
<th>Minimum time period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated 40±2</td>
<td>75±5</td>
<td>6</td>
</tr>
<tr>
<td>Intermediate *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Long-term 30±2</td>
<td>65±5 or 75±5</td>
<td>6</td>
</tr>
</tbody>
</table>

  *Where long-term conditions are 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH, there is no intermediate condition.*
Stability indicating parameters

- Common deficiency:

  Failure to include all stability indicating parameters such as related substances, microbial limit test (MLT).

- Requirement:

  For stability-indicating parameters such as related substances and microbial limits, testing will be performed at release and shelf-life during stability studies.
Photostability data

- Common deficiency:
  Failure to provide photostability data where required

- Requirement:
  photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeia for the API or FPP, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies.
In use stability data

- **Common deficiency:**
  Failure to provide in use stability data (when applicable)

- **Requirement:**
  The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf life.
Ongoing stability studies

Common deficiency:

Failure to provide stability protocol and stability testing commitment for ongoing studies

Requirement:

An ongoing stability programme is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every container closure system, if relevant, should be included in the stability programme (unless none is produced during that year). A written commitment (signed and dated) to this effect should be included in the dossier.
Presentation of data

- Common deficiency:
  Data is provided in such a way that trends cannot be determined, e.g. range of dissolution values but no average, or limits cannot be assessed, e.g. average dissolution but no range of individual values.

- Requirement:
  The actual stability results/reports used to support the proposed shelf-life should be provided. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed at minimum as both the average and range of individual results.
zone IVb climatic conditions

- Common deficiency:

  Failure to conduct studies at zone IVb (Hot and very Humid) climatic conditions of 30± 2°C and 75 ±5%RH.

- Requirement:

  Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied in Climatic Zones III and IV countries.
Effective as of September 2011, the required long-term storage conditions for the Prequalification Programme are 30°C±2°C/75%±5%RH, and after this date the long-term data submitted in the product dossier should be at these conditions. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.
The guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP) has been revised: Preparation of Product Dossiers (PDS) in Common Technical Document (CTD) format

(see link below):
New Generic Guide

- These guidelines have been developed to provide the following:
  
  1) ICH CTD structure has been adopted and the guidelines provide full details on preparation of dossiers in this format.

  2) The quality guideline is more extensive than previous guidelines. The guideline has been updated to reflect current requirements and at the same time, additional details have been provided on how to meet the current requirements.

  3) Certain reductions in requirements are described.
Reduced requirement on Stability

- There is a reduced requirement for the number of FPP batches required to establish the shelf-life, for both complicated FPPs* (minimum three pilot batches reduced to minimum two pilot batches) and uncomplicated FPPs (minimum three pilot batches reduced to minimum one pilot batch and a second batch which may be smaller).

- These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.
Conclusion

- Major challenge:

Determining the authenticity of data submitted! Manufacturers fail to prove stability of their products or even manipulate or fake the raw data!

- Inspectors have to confirm the data submitted during GMP inspections.
END OF PRESENTATION

Thank you