Comparability study to support commercial process change via stability study

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EMA Workshop “Draft Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development”

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This is a joint industry presentation on behalf of the trade associations shown
AGENDA

✓ Regulatory background

✓ Comparability analysis on Stability studies from accelerated/stressed conditions

✓ Comparability analysis on Release data from routine manufacturing
AGENDA

✓ Regulatory background

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✓ Comparability analysis on Release data from routine manufacturing
Regulatory background - ICH Q5E*

PURPOSE
• Comparing post-change product to pre-change product following manufacturing process changes

When considering the comparability of products, the manufacturer should evaluate, for example:
• The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
• Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of pre-change and post-change product.

*Guidance for Industry Q5E Comparability of Biotechnology/Biological Products Subject to Changes in Their Manufacturing Process (June 2005)
Regulatory background – EMA reflection paper*

PURPOSE

• Comparing post-change product to pre-change product following manufacturing process changes

Practical considerations for comparability of products:

• In practice, comparability ranges are frequently established based on a statistical interval, e.g. the min-max range or a tolerance interval calculated from characterization data of the reference product.

• comparison of single batch data to a min-max range might be suitable in the context of batch-release

• A tolerance interval (TI) is usually computed to estimate a data range by which a specified proportion (e.g. the central 90%) of the units from the underlying population is assumed to be covered with a pre-specified degree of confidence (e.g. 95%) … all test batches of the sample fall within the 90%/95% TI computed from the reference batches

*Reflection paper on statistical methodology for the 4 comparative assessment of quality attributes in drug development (March 2017)
AGENDA

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✔ Comparability analysis on Stability studies from accelerated/stressed conditions

✔ Comparability analysis on Release data from routine manufacturing
Comparability pre-/post- change for stability data

General context

Context:
• Process change (ex: new improved process, new site)
• 6 manufactured batches (3 pre- and 3 post- change), consecutive batches are usually chosen for each process
• DS/DS or DP/DP comparability
• Only the stability indicating methods are selected
• Stability at accelerated/stressed condition is performed, duration is chosen so it is representative of the total degradation that will occur at the intended storage condition for the shelf-life period
• Comparability protocol: degradation rate between pre- and post-change batches at accelerated/stressed condition are similar

For major changes in order to reduce the analytical variability:
• Batches are run on stability in parallel
• The stability samples are analyzed in side-by-side analysis (in the same analytical sequence) when feasible.
Comparability pre-/post- change for stability data

Types of comparability

The following types of comparability are done:

- For decreasing or increasing attributes for which sufficient quantifiable data are available (at least 3 time points with values above LOQ by batch): Comparison of slopes and intercepts among processes by mixed effects ANOVA: test for difference

- For increasing attributes with insufficient quantifiable data (less than 3 data points with values above LOQ for at least one batch): Comparison of probability of increased risk of Out Of Specification (OOS) values (between original and new process) and comparison of ranges of values
Comparability pre-/post- change for stability data

Decreasing or increasing attributes with sufficient quantifiable data

For decreasing or increasing attributes for which sufficient quantifiable data are available (at least 3 time points with values above LOQ by batch):

• Estimate degradation rates for each process via a mixed effects ANOVA model
• Use “process” (2 levels: pre- and post- changes process) as a fixed effect, “batch within process” as a random effect, and “time” as a covariate.
• Example of SAS code:

```sas
proc mixed data;
  class batch Process ;
  model response = time   Process   time*Process/s;
  random batch(Process)  time*batch(Process)/s;
run;
```

• A test for slopes and intercepts between process is conducted
Comparability pre-/post- change for stability data
Decreasing or increasing attributes with sufficient quantifiable data

To determine the poolability of different processes the following tests are performed:

1. Test for equality of slopes (“time*Process“)
2. Test for equality of intercepts (“Process“)

Statistical analysis is performed at the significance level of 5% (alpha=0.05)

Based on these hypothesis, three different models can be proposed:

- **Model 1**: Separate slopes and separate intercepts: Degradation profiles of the tested processes are not homogeneous. They differ in their degradation rate.

- **Model 2**: Common slope but different intercepts: Degradation profiles of the tested processes behave the same in their degradation rate but they differ by an offset.

- **Model 3**: Single common regression model: Degradation profiles of the tested processes have a common slope and common intercept. Processes have the same degradation rate.
Comparability pre-/post- change for stability data
Decreasing attributes – case study 1 (Model 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>time*process</td>
<td>0.0259</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

A comparison of degradation slopes at the intended storage condition was also performed with the same methodology and confirmed that slopes are comparable (p-value >0.05)
Comparability pre-/post- change for stability data
Decreasing attributes – case study 2 (Model 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>time*process</td>
<td>0.4050</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>process</td>
<td>0.0459</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Model 2: Common slopes and separate intercepts

=> degradation rates are considered the same

Estimated difference between intercepts:

0.20%

This is within the expected variability between batches

=> intercepts are considered the same
Comparability pre-/post-change for stability data
Decreasing attributes – case study 3 (Model 3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>time*process</td>
<td>0.7576</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>process</td>
<td>0.2567</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

P-value >0.05

Model 3: Single common regression model

=> degradation rates and intercepts are considered the same
Comparability pre-/post- change for stability data
Increasing attribute with values <LOQ

• The **mixed model approach cannot be applied** for increasing attributes for which not sufficient quantifiable data are available (regression cannot be estimated)

• **The comparability between processes is done by comparing:**
  – the number of OOS results versus the number of results within specification at each time point.
  – the range of values from post-change batches with the range of values from pre-change batches

• **If the range of values** from post-change batches is **within or equal** to the range of values from pre-change batches, **process are considered comparable**

• **If the range of values** from post-change batches is **larger than** the range of values from pre-change batches, a **comparison of the observed difference with the analytical variability is made**
Comparability pre-/post- change for stability data
Increasing attribute with values <LOQ

Example: For an increasing attribute, with LOQ=0.4% and Specification=1% the following values were observed:

<table>
<thead>
<tr>
<th>Time point (Months)</th>
<th>Results number</th>
<th>Pre-change process</th>
<th>Post-change process</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In specification</td>
<td>OOS</td>
</tr>
<tr>
<td>0</td>
<td>3 (&lt;LOQ)</td>
<td>0</td>
<td>3 (&lt;LOQ)</td>
</tr>
<tr>
<td>1</td>
<td>3 (&lt;LOQ)</td>
<td>0</td>
<td>3 (&lt;LOQ)</td>
</tr>
<tr>
<td>1.5</td>
<td>3 (&lt;LOQ)</td>
<td>0</td>
<td>3 (&lt;LOQ)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

- Up to 1.5M, all values are below LOQ for both pre- and post-change- process
- At 2M, all values are in specification and observed values for pre-change process are 0.8%, 0.8%, 0.8% and for post-change process are 0.7%, 0.8%, 0.8%.
- At 3M, all values are OOS and observed values for pre-change process are 1.2%, 1.2%, 1.2% and for post-change process are 1.1%, 1.2%, 1.2%.

Process are considered comparable with respect to this attribute
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Comparability pre-/post- change for release data

**Context:**
- Process change (ex: new improved process, new site)
- 3 manufactured batches post-change (validation batches)
- Large pool of historical data (including clinical batches) for pre-change process
- Attributes are divided into three categories:
  1. qualitative attributes
  2. quantitative attributes with values below the limit of quantification (LOQ)
  3. quantitative attributes with values above LOQ.
- Only the quantitative attributes are discussed in this presentation
- Historical ranges are determined as:
  1. min: minimum value observed (or NA); max: maximum value observed (or <LOQ).
  2. Tolerance Intervals (TI) covering 99% of the population with a 95% confidence level.

- **Comparability protocol:** release values for batches post-change are within the historical range for pre-change batches
- **Post change monitoring:** Release values for post-change process are monitored through Continued Process Verification plan, through product lifecycle
Comparability pre-/post-change for release data

- If more than 50% of the observations are below the limit of quantification (LOQ), no statistical analysis is performed; limits are fixed as: min/max.

- If less than 50% of the observations are below the LOQ, individual data reported as below the LOQ are replaced by LOQ \( \frac{1}{\sqrt{2}} \).

- If less than 6 different values are reported for an attribute, limits are fixed as min/max.

- If at least 6 different values are reported for an attributed, the normality is verified using the p-value of Shapiro-Wilk test or Kolmogorov’s D test. If data are normally distributed limits are fixed as 99%95% TI. If data are neither normally distributed nor log-normally distributed, limits are fixed as min/max.

- Outliers are excluded from TI computation (Grubbs test to detect outliers).
Comparability pre-/post-change for release data

Examples

Example 1: Continuous parameter with more than 50% of observations <LOQ
=> Historical limits: min/max = <LOQ/0.5  
post-changes values: <LOQ, <LOQ, <LOQ

Example 2: Continuous parameter with 20% of observations <LOQ;
– Data below LOQ are replaced by \( \text{LOQ} \frac{1}{\sqrt{2}} \),
– Data are not normally nor log-normally distributed

=> Historical limits: min/max = <LOQ/1.4  
post-changes values: 0.6, 0.8, 0.9
Comparability pre-/post- change for release data

Examples

Example 3: Continuous parameter with less than 6 different values (ex: pH)

=> **Historical limits:** min/max = 4.5/4.8

post-changes values: 4.6, 4.6, 4.7

![Histogram for Example 3](image)

Example 4: Continuous parameter with at least 6 different values

=> **Historical limits:** 99%95%TI: [188, 203]

post-changes values: 197, 199, 200

![Histogram for Example 4](image)
TAKE AWAY MESSAGE

• Stability data should be considered for process pre-/post-change comparison.
• Evaluation of stability data at recommended storage conditions would require entire expiry period, for a good estimation of slope and a meaningful comparison. Instead, evaluate stability data at accelerated/stressed condition.
• Accelerated conditions can provide a direct comparison of pre- and post-change product that might not be apparent at lot release or recommended storage.
• For batch release comparability, compute historical ranges (min/max or TI depending on the available data) and compare with release values from validation batches.
Questions...