Further Stability Considerations

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FDA-GPhA Workshop
June 4, 2013
Agenda

• Common considerations
• Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (presented at the FDA-GPhA Spring workshop in 2012); additional recommendations/information
• Q1E Evaluation of stability data – considerations, recommendations
• Summary
Common Considerations

• The specification (tests, and criteria) proposed should be the same for all 3 ANDA submission batches regardless of Bracketing or Matrixing design chosen

• Sterile drug product batches (supporting ANDA submission) should be manufactured in a sterile facility; sterility is a critical product quality attribute

• Time points for various storage conditions:
  – Accelerated time points (4 points): 0, 3, 6, and one point between 3 and 6 months (4 or 5 months)
  – Intermediate time points (0, 6, 9, and 12 months)
  – Long-term time points (0, 3, 6, 9, 12, 18, 24, 36 months)
  – 0 = initial release
Q1D, and Q1E Considerations

• Q1D - Bracketing and Matrixing
  – reduced designs can be applied as a suitable alternative to a full design when multiple factors are involved; reduced designs based on different principles; discuss additional considerations/recommendations

• Q1E – Data analysis
  – All three ANDA submission batch data to be presented; tabular form, graphs (critical product attributes), narrative, and proposed expiration
Drug Product -Bracketing

• No change from current policy – for Bracketing
• Test only the samples on the extremes of certain design factors (container size/fill/strength) at all time points as in a full design
• Bracketing - experience is great!
  – Time-tested in OGD – ANDA Products are already following this concept
  – Reasonably safe design- multiple batches (3)
  – Extremes of design factors (strength/ fill volume/count size) are tested at all times as in a full design
Considerations for Bracketing

- Change in containers/void volume change/wall thickness/geometry – characteristics should be comparable
- If one of the extremes is no longer expected to be marketed study design needs to be maintained to support intermediates
- The shelf-life of the intermediates should not exceed that of the least stable extreme
- Bracketed strength will need initial full release testing, and Biowaiver request (if eligible)
Example of a Bracketing Design

- Q1D

<table>
<thead>
<tr>
<th>Strength</th>
<th>50 mg</th>
<th>75 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Container size</td>
<td></td>
<td></td>
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<tr>
<td>15 ml</td>
<td>T</td>
<td>T</td>
<td>T</td>
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<tr>
<td>100 ml</td>
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<tr>
<td>500 ml</td>
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Matrixing Considerations

• Matrixing can be implemented without a pre-approved protocol – when ICH guidances are implemented.
• Due to data coming from 3 batches, example tables presented in the Q1D guidance can be adopted.
• Assumes stability of each subset of samples tested represents the stability of all samples at a given time point.
• Recommends full testing at certain time points (e.g., 0, 12, 24, 36 months etc.).
• More suitable for long-term testing protocols than accelerated, or intermediate testing.
Matrixing Considerations

- Degree of Reduction from Q1D - Matrixing guidance depends on:
  - Knowledge of data variability
  - Expected stability of the product
  - Availability of supporting data (including pre-formulation studies/excipient compatibility studies/stress studies)
  - Stability differences in the product within factor or among factors
  - Number of combinations in the study
  
  [1/2 reduction could be too much and 3/4 testing may be just enough]
Applicability

- Factors that can be matrixed
  - Batches – common blend
  - Identical formulations
  - Container sizes
  - Fill sizes
  - Closely related formulations (see Q1D) – colorants/flavors
  - Container closure suppliers if justified

- Factors that should not be matrixed
  - Initial and final time points
  - Test parameters (attributes)
  - (Dosage forms)
  - Storage conditions
  - Strengths w/ different formulations (different excipients or different active/excipient ratios)
### Tables 3a and 3b: Examples of Matrixing Designs for a Product With Three Strengths and Three Container Sizes

#### 3a Matrixing on Time Points

<table>
<thead>
<tr>
<th>Strength</th>
<th>Container size</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch 1</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
<td>T3</td>
<td>T1</td>
<td>T2</td>
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<td></td>
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<tr>
<td>Batch 2</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
<td>T3</td>
<td>T1</td>
<td>T2</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch 3</td>
<td>T3</td>
<td>T1</td>
<td>T2</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
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</table>

#### 3b Matrixing on Time Points and Factors

<table>
<thead>
<tr>
<th>Strength</th>
<th>Container size</th>
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<tbody>
<tr>
<td></td>
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<td>B</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>C</td>
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</tr>
<tr>
<td>Batch 1</td>
<td>T1</td>
<td>T2</td>
<td></td>
<td>T2</td>
<td>T1</td>
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<td>T1</td>
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<td>Batch 2</td>
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<td>T3</td>
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<td>T3</td>
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<td></td>
</tr>
<tr>
<td>Batch 3</td>
<td>T3</td>
<td>T2</td>
<td></td>
<td>T2</td>
<td>T3</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
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</tbody>
</table>

**Key:**

<table>
<thead>
<tr>
<th>Time-point (months)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T</td>
<td>T</td>
<td></td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
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<td>T2</td>
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<td>T3</td>
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<td>T</td>
</tr>
</tbody>
</table>

S1, S2, and S3 are different strengths.
A, B, and C are different container sizes.
T = Sample tested
Additional Considerations

• ANDAs with several strengths (e.g., 3 or more than 3)
  – Matrixing designs possible as this example from previous slide (#11) can be duplicated and used
  – Matrixing examples illustrated in the Q1D guidance are all based on 3 batches (are made) for each strength
  – Multiple strengths are to be submitted at the same time in order to use Matrixing designs
  – Multiple strengths divided among original submission and unsolicited amendments may not qualify/be suitable for matrixing protocol
  – Alternatively a suitable Bracketing design can be proposed – to be discussed in the next slide
Q1D Consideration

– Case where common granulation/blend is used (tablet/capsule), is there a need to make three batches of each strength
– The following is our current thinking:
  • Three separate common granulation/blends to be made
  • one batch per ICH (at least of pilot scale) needs to be manufactured comprising of all strengths (using one of the three common blend batches); the other two batches of common granulation/blend can be used for the highest and lowest strength alone; in the event BE studies are done on a different strength (i.e., a strength that is neither highest or lowest), that needs to be included also in the manufacturing
  • Then a Bracketing design can be used to stability test strengths and all (3) batches, where smallest and largest container fill size alone can be subjected
Q1E Considerations

• What are the expectations for data analysis and evaluation? Our thinking is:
  
  – All three batches’ data to be presented
  – Use of Appendix A: Decision Tree for retest period or shelf life estimation (excludes frozen Ds/Dp)
  – Use of tables, narrative, graphs, and analysis where needed to propose expiration dating (DP), and retest date (DS)
  – Graphical format for assay, impurities/deg. p/total impurities, and other critical attributes (e.g., pH), vs. time pts with upper and lower limits
  – Consideration of Significant Change from ICH Q1A(R2) section 2.2.7.1
  – At the time of submission 6 months accelerated data, and 6 months long-term data to be provided for all 3 ANDA submission batches
  – Submission batches should be made under CGMP, and packaged using automated/similar to commercial packaging lines, to provide adequate protection for the DP
Q1 E Consideration

• If 6 months accelerated data fails/significant change occurs, ANDAs will need 6 months 30 °C/65%RH intermediate data on batches at filing time for all 3 ANDA submission batches

• Narrative to be provided addressing the above
Appendix A – Decision Tree for Data Evaluation

- Tabulate and/or plot stability data on all attributes at all storage conditions and evaluate each attribute separately.

- Significant change at accelerated condition within 6 months?
  - Yes
    - Intended to be stored in a refrigerator?
      - Yes
        - No extrapolation; shorter retest period or shelf life and data covering excursions can be appropriate;
        - Statistical analysis if long-term data show variability.
      - No
        - No extrapolation; shorter retest period or shelf life can be appropriate;
        - Statistical analysis if long-term data show variability.
    - No
      - Long-term data show: (1) little or no change over time and (2) little or no variability?
        - Yes to both
          - No extrapolation; shorter retest period or shelf life can be appropriate;
          - Statistical analysis if long-term data show variability.
        - No to (1) or (2) or both
          - (1) Long-term data amenable to statistical analysis and (2) statistical analysis performed?
            - Yes to both
              - Statistical analysis is normally unnecessary.
            - No to (1) or (2)
              - Accelerated data show: (1) little or no change over time and (2) little or no variability?
                - Yes to both
                  - No extrapolation; shorter retest period or shelf life can be appropriate;
                  - Statistical analysis if long-term data show variability.
                - No to (1) or (2) or both
                  - If backed by relevant supporting data: Y = up to X + 3 months.

- Y = Proposed retest period or shelf life
  - X = Period covered by long-term data

- If backed by statistical analysis and relevant supporting data: Y = up to 2X, but not exceeding X + 12 months; or if refrigerated, Y = up to 1.5X, but not exceeding X + 6 months.

- If backed by relevant supporting data: Y = up to X + 6 months; or if refrigerated, Y = up to X + 3 months.
Q1 E Considerations

- Statistical analysis need not be performed when 6 months accelerated data show no significant change and long term data show no variability. A stable drug product meeting the above will not require statistical analysis, per Appendix A.

- OGD will continue to grant 24 months tentative expiry based 6 months accelerated, and 12 months (or more if available) long-term data (if the above is met).

- Significant change occurs between 0 and 6 months, long-term data needs to be used for analysis and intermediate data are required (30°C/65% RH – 6 months at the time of ANDA submission, and 12 months’ to be amended).
Intermediate Data Evaluation

• 6 months at filing (0/initial, and 6)
• If intermediate data also fails (meaning significant change at that condition)
  - No extrapolation of shelf-life/retest date
  - Long-term data alone will take over shelf-life/retest determination
Q1E Continued

General approach – When stat. analysis is needed
  – Boxes in the Appendix A cite stat. evaluation, and when data shows variability

• Data evaluation approaches
  Linear, logarithmic etc.; long-term data
  -If the relationship is linear between attribute and time then linear regression is a preferable mode
  -Linear regression model is popular and applicable when linear potency loss or increase in degradation observed
Data Analysis Expectation

– Plot the long-term data for a given attribute (e.g. assay) vs. time (in months) for 3 batches
– Determine the time when 95% confidence interval intersects the proposed acceptance criteria
– Determine if data are poolable
– Significance level (p) taken into account
– Individual batches are to be used and shortest expiry needs to be proposed
Graph Expectations

• One-sided 95% Confidence limit curve when time vs. acceptance criterion is plotted; at times two-sided will be needed

• Data poolable vs. non poolable
  – Small batch to batch variability = poolable
  – Large variability = not poolable
  – In general common slopes and a common time-zero intercept may mean that data from batches can be pooled
Data Presentation of Long-Term Stability Data
Data Presentation
Data Presentation for Degradation Product

Figure 2

Shelf life Estimation with Upper Acceptance Criterion Based on a Degradation Product at 25C/60%RH

- Raw Data
- Upper confidence limit
- Regression line
- Upper acceptance criterion: 1.4
Q1E Continued

• Setting Expiration (Drug product)

• Retest date (Drug substance)
  – Long-term data to be used for stat. analysis
    • Data amenable to statistical analysis (2 times LT but not more than 12 months, and if refrigerated NMT 6 months)
    • Data not-amenable to statistical analysis (1.5 times LT, but not more than 6 months and if refrigerated NMT 3 months)
Summary

• Key considerations
  – Developing a stability protocol utilizing Q1 D (Bracket or Matrix) guidance is essential to a successful program
  – Application of significant change, generation of ICH intermediate condition data (when needed), and utilization of all 3 batches’ stability data
  – Stable drug product (6 months 40°C/75%RH, and no variability at long-term) will not need data analysis
  – Narrative, and graphical presentation of data (in addition to tables, where assay, impurities can be plotted individually), needed
  – Data analysis needed as indicated by Appendix A – when products experience significant change, using long-term data tentative expiration is to be proposed
Acknowledgements

- Stability WG members: Drs. Atwal, Patankar, Murali, Takiar, and Rajagopalan
- Drs. L. Yu, K. Webber, & Mr. Clark
- Drs. Holcombe, Jr., Raw, Skanchy, Schwartz, Sayeed, and Rosencrance; Mr. Smith, and Mr. Iser
- Dr. Christensen
- FDA, & GPhA