A Step-wise Procedure for Population Bioequivalence (PBE) Analysis of Orally Inhaled and Nasal Drug Product (OINDP) Bioequivalence Studies

Breakout Session:
Inhalation Product Update

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Looking Back…

• Oct. 28, 2009, GPhA/FDA 2009 Fall Technical Conference:
  – Presented “Introduction to a Standardized Bioequivalence Review Procedure for Nasal Spray Products: Review Template and CTD Data Summary Tables”
  – Subsequently, 40 CTD tables published on the FDA public website
    • Positive feedback from industry
    • Average review time of the BE portion of a nasal spray product has been reduced from ~5 weeks to ~2 weeks currently (internal DB reviewer survey)
Today, I am going to introduce…

A Step-wise Procedure for Population Bioequivalence (PBE) Analysis of Orally Inhaled and Nasal Drug Product (OINDP) Bioequivalence Studies
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Background

• Population Bioequivalence (PBE) has been widely utilized as the key statistical approach for many in vitro BE evaluations of OINDP
  – For nasal drug products, out of the 6 in vitro BE studies recommended by the draft Nasal BA/BE guidance, 4 of the tests are evaluated using PBE
  – For oral inhalation drug products, the majority of the recommended in vitro tests will be evaluated using PBE
Population Bioequivalence (PBE) Criterion

- The PBE criterion and BE limit are:

\[
\frac{\mu_T - \mu_R}{\sigma_{R}^2} + \frac{\sigma_{T}^2 - \sigma_{R}^2}{\sigma_{R}^2} \leq \theta_p \quad \text{or} \quad \frac{\mu_T - \mu_R}{\sigma_{T0}^2} + \frac{\sigma_{T}^2 - \sigma_{R}^2}{\sigma_{T0}^2} \leq \theta_p
\]

- Linearized criteria:

\[
\eta_1 = \left(\mu_T - \mu_R\right) + \left(\sigma_{T}^2 - \sigma_{R}^2\right) \cdot \theta_p \cdot \sigma_{R}^2 < 0 \quad \text{for} \quad \sigma_R > \sigma_{T0}
\]

\[
\eta_2 = \left(\mu_T - \mu_R\right) + \left(\sigma_{T}^2 - \sigma_{R}^2\right) \cdot \theta_p \cdot \sigma_{T0}^2 < 0 \quad \text{for} \quad \sigma_R \leq \sigma_{T0}
\]

Where:

- \(\mu_T - \mu_R\) : Mean difference of T (log scale) and R (log scale) products
- \(\sigma_{T}^2, \sigma_{R}^2\) : Total variance of T and R products
- \(\sigma_{T0}\) : Regulatory constant (\(\sigma_{T0}= 0.1\))
- \(\theta_p\) : Regulatory constant (\(\theta_p= 2.0891\) calculated as: \(\frac{[\ln(1.11)]^2 + 0.01}{0.1^2} = 2.089\))
Two FDA Guidances Related to PBE

1. **Statistical Information from the June 1999 Draft Guidance and Statistical information for in vitro bioequivalence data posted on August 18, 1999** (refers as 1999 guidance)


   – Provides general information about the equivalence criteria in analyzing in vivo or in vitro BE studies of various types of applications
## Comparison of the Two Guidances

<table>
<thead>
<tr>
<th>1999 Guidance (draft)</th>
<th>2001 Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 95% upper confidence bound is calculated based procedures outlined in a published paper*, and the difference of the mean of T and R is calculated using Behrens-Fisher method, which involves rather complicated calculation steps</td>
<td>The 95% upper confidence bound is calculated using the simplified T-distribution for the difference of the mean of T and R</td>
</tr>
</tbody>
</table>

Issues

• Up to current, the method described in the 1999 guidance has been routinely used for regulatory review of OINDP drug products

• However, since it involves rather complicated computation, it had led to many inquiries for clarification from sponsors
Inquiries from Industry

• “We worked through the guidance and also read the guidances on statistic evaluation of bioequivalence studies. Where can we get further advice on study design and especially on statistics and statistical evaluation? How is population BE established and verified?”

• “What acceptance criteria were applied to the determination of PBE? Would a copy of the calculation be provided to us?”

• “Could the FDA confirm the formula we have used in our analysis for the calculation of the confidence interval? Could the Agency send us a breakdown of the results for the population bioequivalence analysis?”
An FDA Working Group Was Formed…

– To select a simplified method in the evaluation of PBE for OINDP without compromising the rigor of the regulatory decision

– To provide specific recommendations related to the application of PBE for the evaluation of in vitro equivalence studies of OINDP

– To publish a step-wise set of instructions regarding PBE analysis computation procedures in FDA’s public website
Comparison of the Two Methods

• Simulation Study:
  – Conducted under different scenarios
    • geometric mean differences of T and R ranged from 0 to 20%
    • overall variability differences of T and R ranged from 0 to 30%
  – Data were analyzed by these two methods under different scenarios
  – For estimation of power, 5000 simulations were conducted
Comparison of the Two Methods: Simulation Study Example
Comparison of the Two Methods: Simulation Study Example

<table>
<thead>
<tr>
<th>N</th>
<th>Type I error (2001 method)</th>
<th>Type I error (1999 method)</th>
<th>Life stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>0.0555</td>
<td>0.0626</td>
<td>1</td>
</tr>
<tr>
<td>5000</td>
<td>0.0538</td>
<td>0.0542</td>
<td>2</td>
</tr>
<tr>
<td>5000</td>
<td>0.0550</td>
<td>0.0558</td>
<td>3</td>
</tr>
</tbody>
</table>
Comparison of the Two Methods: Simulation Study Example

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>0.973</td>
<td>0.979</td>
<td>1</td>
</tr>
<tr>
<td>1000</td>
<td>0.973</td>
<td>0.973</td>
<td>2</td>
</tr>
<tr>
<td>1000</td>
<td>0.974</td>
<td>0.975</td>
<td>3</td>
</tr>
</tbody>
</table>
Comparison of the Two Methods

• Real ANDA Study:
  – Two methods were compared using three ANDAs representing different drug products
  – A typical design for nasal/inhalation products was used, i.e., the in vitro studies were conducted using 3 batches and 10 containers per batch for each T and R
  – Comparisons were conducted for various in vitro BE studies at different life stages of the drug products, such as beginning, middle and end
Comparison of the Two Methods: Real Case Example

<table>
<thead>
<tr>
<th>ANDAs</th>
<th>Constant Scale 95% Upper Confidence Bound</th>
<th>Reference Scale 95% Upper Confidence Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA 1 Test 1</td>
<td>-0.0189109</td>
<td>-0.01891049</td>
</tr>
<tr>
<td>ANDA 1 Test 2</td>
<td>-0.017962848</td>
<td>-0.017962549</td>
</tr>
<tr>
<td>ANDA 1 Test 3</td>
<td>0.015677416</td>
<td>0.015695358</td>
</tr>
<tr>
<td>ANDA 1 Test 4</td>
<td>0.030507028</td>
<td>0.030507958</td>
</tr>
<tr>
<td>ANDA 2, Test 5</td>
<td>-0.02170561</td>
<td>-0.021700441</td>
</tr>
<tr>
<td>ANDA 2, Test 6</td>
<td>-0.014457372</td>
<td>-0.014455345</td>
</tr>
<tr>
<td>ANDA 2, Test 7</td>
<td>-0.024330906</td>
<td>-0.02432152</td>
</tr>
<tr>
<td>ANDA 2, Test 8</td>
<td>-0.0158553897</td>
<td>-0.015854909</td>
</tr>
<tr>
<td>ANDA 3, Test 9</td>
<td>-0.018910889</td>
<td>-0.01891049</td>
</tr>
</tbody>
</table>
## Comparison of the Two Methods: Real Case Example

<table>
<thead>
<tr>
<th>ANDAs</th>
<th>PBE Outcome Constant Scale</th>
<th>PBE Outcome Reference Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA 1 Test 1</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>ANDA 1 Test 2</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>ANDA 1 Test 3</td>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>ANDA 1, Test 4</td>
<td>Fail</td>
<td>Fail</td>
</tr>
</tbody>
</table>
Results from a simulation study showed the type I error for the two methods are similar.

Results from both simulation studies and real ANDA data showed the values for the 95% upper confidence bound calculated by the two methods are nearly identical; differences appear at the fifth digit after the decimal point.

The real ANDA data showed the overall conclusions (e.g., pass or fail PBE) are the same for these two methods.
Conclusions

- Comparable PBE results are obtained by these two different methods.

- 2001 method provides a simplified alternative to 1999 method without compromising the rigor of the regulatory decision.

- Based the study results, the 2001 method is recommended for PBE analysis in the evaluation of PBE for OINDP.
Firm’s Inquiry

Could the Agency send us a breakdown of the results for the population bioequivalence analysis?
FDA’s Response

FDA is developing a step-wise computation procedures for PBE analysis using 2001 method

- **Step 1**: Establish population BE criterion
- **Step 2,3,4**: Calculate intermediate parameters
- **Step 5**: Determine bioequivalence
Firm’s Inquiry

• Would a copy of the calculation be provided to us?

• Could the FDA confirm the formula we have used in our analysis for the calculation of the confidence interval?
FDA’s Response

FDA will provide an example data set for confirmation purpose

• In order for the applicants to confirm their calculation procedures, OGD will provide an example data set, to demonstrate the calculation outcomes of each intermediate and final step

• The applicants can use the data shown in our example, and follow the step-wise computation procedures, to check whether they obtain the same outcomes as indicated in our example
Common Technical Document (CTD) Tables

- FDA has also developed a set of CTD tables to be used to submit the in vitro data applied in PBE analysis
  - To guide pharmaceutical industry in submitting their data in an appropriate format
  - To reduce the time of reviewing process, therefore, improve the review efficiency and quality
Example of CTD Table:
Single Actuation Content through Container Life

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SECTOR</th>
<th>LOT</th>
<th>CONTAIN</th>
<th>ACTUAT</th>
<th>AMOUNT</th>
<th>PCTLABEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST</td>
<td>B</td>
<td>1234</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>4</td>
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<tr>
<td></td>
<td></td>
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<td>5</td>
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<td>…</td>
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<td></td>
</tr>
</tbody>
</table>

* Terms in this table are defined in the next slide
### Example of CTD Table: Single Actuation Content through Container Life

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Variable Label</th>
<th>Variable Type</th>
<th>Content</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODUCT</td>
<td>Product Name</td>
<td>Character</td>
<td>TEST or REF</td>
<td>Identifier for product</td>
</tr>
<tr>
<td>SECTOR</td>
<td>Lifestage</td>
<td>Character</td>
<td>B, or E</td>
<td>B=Beginning; E=End</td>
</tr>
<tr>
<td>LOT</td>
<td>Lot number</td>
<td>Alphanumeric</td>
<td>Alphanumeric</td>
<td>Identifier for product lot</td>
</tr>
<tr>
<td>CONTAIN</td>
<td>Bottle or container Number</td>
<td>Numeric</td>
<td>Numeric values</td>
<td>Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).</td>
</tr>
<tr>
<td>ACTUAT</td>
<td>Spray Number</td>
<td>Numeric</td>
<td>Numeric values</td>
<td>Actual spray number corresponding to B or E life stages.</td>
</tr>
<tr>
<td>AMOUNT</td>
<td>Actual delivered amount of drug mass</td>
<td>Numeric</td>
<td>Numeric values</td>
<td>Drug mass per single actuation</td>
</tr>
<tr>
<td>PCTLABEL</td>
<td>Percentage of label claim</td>
<td>Numeric</td>
<td>Numeric values</td>
<td>Percentage of drug mass per single actuation</td>
</tr>
</tbody>
</table>
Where to Find This Information

• OGD has published the CTD data format tables, designed for nasal product application, at FDA public website: http://wcms.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm?SSContributor=true

• OGD is currently working on the development of the step-wise procedures for PBE analysis
Conclusions

• FDA has selected a simplified method for PBE analysis for the in vitro BE studies of OINDP products
• FDA is developing a step-wise instruction with computation procedures for the PBE analysis using the selected method
• FDA has developed a set of CTD tables to guide the industry to submit higher quality application
• FDA plans to make this information available to the public
Acknowledgements

- Yaning Wang
- Wallace Adams
- Sau (Larry) Lee
- Devvrat Patel
- Dale Conner
- Hoainhon Caramenico
- Barbara Davit