A Real Case Comparison of Average and Population Bioequivalence for Evaluation of APSD data

IPAC-RS/UF Orlando Inhalation Conference
March 18-20, 2014
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• The data – brief review
• Average & Population Bioequivalence
• Comparing TEST and REF
• Simulation model
• Probability to pass PBE
• Adjusting ABE to match PBE
• Conclusions
The data

- Real APSD data used as illustration
- Many thanks to the donating company!
- NGI data comparing “generic” multi-dose DPI to the corresponding innovator product
- 3 different strengths
- 3 flow rates (at 2, 4 & 8 kPa)
- 3 TEST batches, 4 REF batches
- 6 NGIs per batch
- Total of $3 \times 3 \times (3+4) \times 6 = 378$ NGIs
- Data normalized to target delivered dose
The data, cont’

• First want to show a few slides to get familiar to the data set
• Match to target delivered dose (DD)?
• Flow dependence?
• Strength differences?
• TEST/REF APSD relations?
Total dose at 4 kPa

- Total dose (TD) = T+PS+S1+ ... +S7+MOC
- Table shows average TD (% target DD) for each batch
- REF batches about 15% below target
- TEST batches only 3% lower
- This difference will make it hard to show equivalence

<table>
<thead>
<tr>
<th>Strength</th>
<th>REF</th>
<th>TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td>R2</td>
<td>T2</td>
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<tr>
<td></td>
<td>R3</td>
<td>T3</td>
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<tr>
<td></td>
<td>R4</td>
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<tr>
<td>LOW</td>
<td>80</td>
<td>99</td>
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<td></td>
<td>79</td>
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<td>MID</td>
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<td>96</td>
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<tr>
<td>HIGH</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>96</td>
</tr>
</tbody>
</table>

Strength:
- LOW
- MID
- HIGH

REF:
- R1
- R2
- R3
- R4

TEST:
- T1
- T2
- T3

Real case: ABE vs PBE for APSD
Flow dependence (TD)

<table>
<thead>
<tr>
<th>Strength</th>
<th>REF</th>
<th>TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 kPa</td>
<td>4 kPa</td>
</tr>
<tr>
<td>LOW</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>MID</td>
<td>75</td>
<td>87</td>
</tr>
<tr>
<td>HIGH</td>
<td>69</td>
<td>84</td>
</tr>
<tr>
<td>ALL</td>
<td>71</td>
<td>86</td>
</tr>
</tbody>
</table>

- Table shows average TD for each combination of strength and flow rate (average of corresponding batch averages)
- TEST product almost flow independent
- REF product 15% lower at 2 kPa and 10% higher at 8 kPa
- Will be difficult to show equivalence at all flow rates
- Would relaxed requirements at 2 & 8 kPa be appropriate?
Comparison of strengths (4 kPa)

- For both TEST and REF only marginal strength differences - both products have excellent dose proportionality
- Majority of drug in throat & pre-separator
- Almost nothing at S1, S7 & MOC
- Some apparent product differences for coarser particles
TEST vs. REF: all raw data (4 kPa)

- All strengths pooled in graph – individual results shown
- Apart from T+PS the relation looks very good (i.e. T/R = 1)
- REF slightly higher for S3-S5?
TEST/REF ratio by stage and flow

- Pooled strengths in graph for overview
- T/R profile fairly stable over full flow range studied
- Average relation within 75-125% for S2-S6 for all flow rates
- Clearly not possible to show IVBE for most stages

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Real case: ABE vs PBE for APSD
Formal comparison

• Selected 5 parameters:
  – Total dose (TD; T+PS+S1+ ... + S7+MOC)
  – Coarse particle dose (CPD; T+PS)
  – Fine particle dose (FPD; particles <5 μm)
  – MMAD and GSD.

• Compare TEST to REF for each strength and flow rate (3 x 3 x 5 = 45 tests)

• Use both average & population BE methods
Average bioequivalence (ABE)

• We want to make a 90% confidence interval (CI) for the mean TEST/REF ratio
• One approach:
  – TEST: $x_{ij} = \log(X_{ij})$; denote by $n_x$, $m_x$ and $s_x$ the sample size, average and std, respectively, of log-transformed data
  – REF: corresponding notation ($n_y$, $m_y$ and $s_y$)
  – 90% CI for difference between log means: $(ll, ul) = m_x - m_y \pm t \cdot S$, where
    • $t = t_{0.05}(n_x + n_y - 2)$ quantile from t-distribution
    • $S^2 = \frac{[(n_x-1)s_x^2 + (n_y-1)s_y^2] / (n_x + n_y - 2)}{n_x + n_y - 2}$ pooled variance estimate
  – 90% CI for ratio (% scale):
    • $LL = 100 \cdot \exp(ll)$; $UL = 100 \cdot \exp(ul)$
• Claim bioequivalence if $(LL, UL)$ contained in $(85, 118)$
• $118 = 100 / [(100 - 15) / 100]$
• Interval based on regulatory constant ($\pm 15\%$) in reference [1]
ABE: 90% CIs

- All 45 CIs in one graph
- 5 panels, one for each parameter
- Grouped by flow rate (2 kPa left, 6 kPa right) and colored by strength
- MMAD & GSD pass; FPD & TD borderline
- CPD clearly different

Real case: ABE vs PBE for APSD
Population bioequivalence (PBE)

• We want to make an upper limited 95% confidence interval for $\omega$, where

$$\omega = (\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2) - \theta_p \max \{\sigma_{T0}^2, \sigma_R^2\}$$

• Here $\mu_T$ and $\sigma_T$ denote the mean and STD for the TEST product (log scale); similar for REF

• $\sigma_{T0} = 0.1$ and $\theta_p = 2.0891$ are regulatory constants

• Construction of CI long-winded; see reference [2]

• Claim bioequivalence if upper limit < 0
PBE: 95% CIs

- Very consistent compared to ABE analysis (only in one case the two approaches resulted in different conclusion)
- MMAD & GSD pass; FPD and TD close, CPD far off
- With increased sample size all parameters but CPD and TD at 2 kPa will pass (as will happen for ABE)
Summary so far

• PBE and ABE seem to result in same conclusion for these data
• But this is not so strange when the TEST/REF ratio is far off 100%
• Let us assume TEST/REF = 100%
• What is the acceptance criteria for ABE that result in the same chance to pass as the probability to pass PBE?
• Study this by simulation
Simulation approach

• Use REF product data for all strengths and flow rates
• Log-transform data
• For each strength, flow rate & NGI stage, calculate overall mean and STD between and within batch
• Based on these and assuming a normal distribution, generate 6 batches with 10 results each (for each stage)
• Denote 3 of them ”TEST” and the other 3 ”REF”
• Check if data fulfill PBE acceptance criteria
• Repeat many times to obtain estimate of probability to pass PBE (in each of the 3 x 3 x 9 = 81 cases)
• Then determine ABE acceptance criteria to match PBE pass rate (again using simulation)
Example for LOW strength at 4 kPa

- P(pass PBE) estimates based on 10,000 simulations per parameter
- Results indicates that (for this product) the chance that REF fulfill PBE equivalence to itself for individual stages typically is <<100%
- Perhaps regulatory PBE constants need to be re-considered?
- But question here is what ABE acceptance criteria would match the obtained PBE pass rates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Between batch STD</th>
<th>Within batch STD</th>
<th>P(pass PBE) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+PS</td>
<td>3.530</td>
<td>0.088</td>
<td>0.112</td>
<td>67</td>
</tr>
<tr>
<td>S1</td>
<td>-0.043</td>
<td>0.124</td>
<td>0.116</td>
<td>58</td>
</tr>
<tr>
<td>S2</td>
<td>1.635</td>
<td>0.169</td>
<td>0.116</td>
<td>52</td>
</tr>
<tr>
<td>S3</td>
<td>2.397</td>
<td>0.100</td>
<td>0.095</td>
<td>62</td>
</tr>
<tr>
<td>S4</td>
<td>2.771</td>
<td>0.064</td>
<td>0.078</td>
<td>87</td>
</tr>
<tr>
<td>S5</td>
<td>2.444</td>
<td>0.049</td>
<td>0.077</td>
<td>95</td>
</tr>
<tr>
<td>S6</td>
<td>1.473</td>
<td>0.029</td>
<td>0.080</td>
<td>100</td>
</tr>
<tr>
<td>S7</td>
<td>0.051</td>
<td>0.000</td>
<td>0.095</td>
<td>99</td>
</tr>
<tr>
<td>MOC</td>
<td>-0.943</td>
<td>0.104</td>
<td>0.175</td>
<td>72</td>
</tr>
</tbody>
</table>
P(pass ABE) vs. acceptance limit

- Determine P(pass ABE) for gradually increasing acceptance intervals
- Graph shows that the chance to pass is $<<100\%$ for several individual stages when using EU guidance acceptance limit of $\pm 15\%$
- For example for S2 an ABE acceptance limit of $> 30\%$ is needed for 100% pass chance

[Graph showing the relationship between acceptance limit and P(pass ABE)]
ABE acceptance limit to match PBE pass

• Use graph to determine what ABE acceptance limit that would give same pass rate as PBE test

• Surprisingly good match!

• Associated ABE acceptance limit typically slightly lower than standard ±15%

• PBE slightly more stringent (except for S2 & MOC)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P(pass PBE) (%)</th>
<th>ABE acceptance limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+PS</td>
<td>67</td>
<td>13</td>
</tr>
<tr>
<td>S1</td>
<td>58</td>
<td>14</td>
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<tr>
<td>S2</td>
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<td>S3</td>
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<td>S4</td>
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<td>S5</td>
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<td>12</td>
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<tr>
<td>S7</td>
<td>99</td>
<td>10</td>
</tr>
<tr>
<td>MOC</td>
<td>72</td>
<td>17</td>
</tr>
</tbody>
</table>
Same analysis for all REF data

- PBE pass rate for all strengths, flow rates and individual stages
- Pass rates typically 50-100% - seldom reaching 100% (only 20 of 81 > 95%)
- No consistent difference between strengths or flow rates
- Lower pass rates for S1, S2, S7 and MOC – these are stages with lowest mean and/or highest STDs
• Probability to pass generally decreases with increasing STD – as expected
• Relation is not very robust for larger STDs (too small sample size?)
• With a total STD <0.10 (of log data) the chance to pass PBE is > 90%
ABE acceptance limit to match PBE pass

- Matching ABE acceptance limit is typically slightly below 15% - PBE is a tighter test
- Not true for MOC and a few single other cases – why?
- How is matching limit related to total variability in parameter?
Matching acceptance limit vs. total STD

- Strong relation! ABE acceptance limit = 4.9 + 61 × STD
- ABE and PBE are equally tight if total STD = 0.166 (for log data)
- Remember that we study the comparison REF vs. REF
- Relation holds for this test plan (3 x 10 units) – true for other too?
Conclusions (1)

• Real data from a TEST/REF DPI comparison has been reviewed
• 3 strengths and 3 flow rates; 378 NGIs
• ABE and PBE evaluations for key parameters give almost identical conclusions (44 of 45 tests)
• Simulation study (3 x 10) based on REF data
• Pass rates are typically 50-100%; decreasing with increasing total STD
• The analysis shows that for most individual stages there is a high risk that REF would fail PBE when compared to itself
• This strongly suggests that PBE regulatory constants should be re-considered
Conclusions (2)

• ABE acceptance limits to match PBE pass rates are typically slightly below ±15%
• PBE is thus "usually" a tighter requirement
• Exceptions exist (MOC – high variability)
• Matching ABE acceptance limit linearly related to total STD
• If total STD of log-transformed data > 0.166 ABE is tighter, otherwise PBE is a more stringent requirement
• The above holds when a product is compared to itself & for the common test plan of "3 batches & 10 units per batch"
• Similar conclusions are expected for alternative test plans
• When TEST and REF have different characteristics the ABE/PBE relation is likely more complex
References
