The Modified Chi-Square Ratio Statistic for Equivalence Testing of Aerodynamic Particle Size Distribution

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IPAC-RS/UF Orlando Inhalation Conference
March 19, 2014
Disclaimer

This presentation was prepared by Benjamin Weber and Renish Delvadia and reflects their views and should not be construed to represent views or policies or opinions from Boehringer Ingelheim or FDA.

Benjamin Weber was not involved in any work that was performed by Renish Delvadia after March 2013.
Where Do We Stand?

• The modified chi-square ratio statistic (mCSRS) approach is a promising approach for equivalence testing of aerodynamic particle size distribution (APSD)

• The robustness, sensitivity, and the capability of discriminating between equivalent and inequivalent impactor profiles has been demonstrated

Open Questions (March 2013)

- Determination of cut-off value for APSD equivalence testing
- Construction of confidence intervals for MmCSRS
  - One-sided vs. two-sided
- Influence of inter-site correlation structure on MmCSRS
- Best metric for reference variance scaling?
Outline

1. Review properties of mCSRS
2. Visualization of stepwise APSD equivalence testing approach and calculation of mCSRS including construction of confidence intervals
3. Selection of optimal reference scaling approach (RSA) and classification of PQRI CI scenarios (work performed by R. Delvadia)
KEY PROPERTIES OF MODIFIED CHI-SQUARE RATIO STATISTIC
Modified Chi-Square Ratio Statistic

\[
mCSRS_{jk} = \frac{\sum_{i=1}^{p} \frac{(T_{ij} - \bar{R}_i)^2}{\bar{R}_i}}{\sum_{i=1}^{p} \frac{(R_{ik} - \bar{R}_i)^2}{\bar{R}_i}}
\]

- \( p \): number of deposition sites
- \( T_{ij} \): deposition (%) on \( i^{th} \) site of \( j^{th} \) T sample
- \( R_{ik} \): deposition (%) on \( i^{th} \) site of \( k^{th} \) R sample
- \( \bar{R}_i \): average deposition on \( i^{th} \) site of all R samples
Key Properties of mCSRS

• Modified chi-square ratio statistic (mCSRS) is a sensitive and robust metric for comparative cascade impactor (CI) analysis

• Median of the distribution of mCSRSs (MmCSRS) is equal to one when test (T) and reference (R) CI profiles are identical regardless of the shape and number of deposition sites
Key Properties of mCSRS

- MmCSRS is more sensitive to differences on high deposition sites when T and R CI profiles differ from each other.
- MmCSRS is dependent on the variability of R product.
- Cut-off value for equivalence testing requires scaling on the variability of the R product.
Visualization

PROPOSED APSD EQUIVALENCE TEST AND MMCSRS
APSD EQUIVALENCE TESTING METHOD

APSD Equivalence Test

Total Mass – mean (sd)
Ref: 234.4 mcg (10.26)
Test: 235.9 mcg (8.71)
PBE < 0 => pass

ISM – mean (sd)
Ref: 67.7 mcg (6.39)
Test: 66.7 mcg (6.58)
PBE < 0 => pass

\[
\sum_{i=1}^{7} M_M \cdot m_C \quad \sum_{i=1}^{7} M_M = 18.77 \quad \Rightarrow 20\% \text{ acceptance in critical value plot}
\]

\[
\text{Sum} = 2.11
\]
Modified Chi-Square Ratio Statistic

\[ mCSRS_{jk} = \frac{\sum_{i=1}^{p} \frac{(T_{ij} - \bar{R}_i)^2}{\bar{R}_i}}{\sum_{i=1}^{p} \frac{(R_{ik} - \bar{R}_i)^2}{\bar{R}_i}} = \frac{2.60}{2.11} = 1.23 \]
mCSRS – Algorithm

30 T

30 R

900 Pairs (30 T * 30 R)

900 mCSRS

MmCSRS = 1.08

Median
Bootstrapping (simplified)

• Create 2,000 sets of 30 T and 30 R samples by resampling (with replacement) from set of original 30 T and 30 R samples
• Calculate MmCSRS for each of the 2,000 sets
• Cut-off lower and upper 5% percentiles of distribution of 2,000 MmCSRSs
• => non-parametric 90% confidence interval for MmCSRS = 0.76 – 1.34
• Upper bound (1.34) smaller than 2.47 (20% acceptance criterion) => equivalent

In practice, a bias-corrected and accelerated (BCA) bootstrapping method is applied
Author: Renishkumar Delvadia, PhD.
Food and Drug Administration
Rockville, MD

SELECTION OF OPTIMAL REFERENCE SCALING APPROACH (RSA) AND CLASSIFICATION OF PQRI CI SCENARIOS
Critical Value Plot

- MmCSRS determined for scenarios with fixed mean % deposition differences in each deposition site between normalized T and R profiles, both having same CV for all deposition sites
- MmCSRS plotted against corresponding CV^2

<table>
<thead>
<tr>
<th>% Difference</th>
<th>intercept</th>
<th>slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>0.9935</td>
<td>123.83</td>
</tr>
<tr>
<td>15%</td>
<td>0.9696</td>
<td>294.00</td>
</tr>
<tr>
<td>20%</td>
<td>0.9489</td>
<td>535.92</td>
</tr>
<tr>
<td>25%</td>
<td>0.9155</td>
<td>856.40</td>
</tr>
<tr>
<td>30%</td>
<td>0.8964</td>
<td>1244.54</td>
</tr>
</tbody>
</table>

- In real life CI profiles have difference CV for each deposition site
- To use critical value plot, a single CV value representing overall variability of reference CI profiles is needed.
# List of RSAs Evaluated

<table>
<thead>
<tr>
<th>RSA</th>
<th>Total number of sites considered in RSA</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSA2</td>
<td>2</td>
<td>Mean of CVs of first 2 HSDs</td>
</tr>
<tr>
<td>RSA3</td>
<td>3</td>
<td>Mean of CVs of first 3 HSDs</td>
</tr>
<tr>
<td>RSA4</td>
<td>4</td>
<td>Mean of CVs of first 4 HSDs</td>
</tr>
<tr>
<td>RSA5</td>
<td>5</td>
<td>Mean of CVs of first 5 HSDs</td>
</tr>
<tr>
<td>RSA6</td>
<td>6</td>
<td>Mean of CVs of first 6 HSDs</td>
</tr>
<tr>
<td>RSA7</td>
<td>7</td>
<td>Mean of CVs of first 7 HSDs</td>
</tr>
<tr>
<td>RSA8</td>
<td>8 (all)</td>
<td>Mean of CVs of first 8 HSDs</td>
</tr>
<tr>
<td>RSA.meanCV</td>
<td>8 (all)</td>
<td>$\frac{\sum_{i=1}^{8} (D_i \times CV_i)}{\sum_{i=1}^{8} D_i}$</td>
</tr>
<tr>
<td>RSA.meanCV²</td>
<td>8 (all)</td>
<td>$\sqrt{\frac{\sum_{i=1}^{8} (D_i \times CV_i^2)}{\sum_{i=1}^{8} D_i}}$</td>
</tr>
</tbody>
</table>

$D_i = \%$ deposition on $i^{th}$ deposition site; HSD — highest deposition sites
$CV_i = \%$ CV of $i^{th}$ deposition site
Evaluation of RSAs: Method

30 T and 30 R profiles with realistic CVs, 30% TR deposition differences

MmCSRS for simulated set of T,R profiles

RSA CV – Single representative CV for realistic CV scenario

Back calculated CV

MmCSRS

Observed MmCSRS

Back calculated CV

\( y = 0.985x \)

\( R^2 = 0.99 \)

(1000 realistic CV scenarios)
Evaluation of RSAs: Results
(30% T and R Difference)

<table>
<thead>
<tr>
<th>RSA</th>
<th>Slope</th>
<th>$R^2$</th>
<th>Residual error</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSA2</td>
<td>0.388</td>
<td>0.2065</td>
<td>2.548</td>
</tr>
<tr>
<td>RSA3</td>
<td>0.5163</td>
<td>0.2339</td>
<td>2.883</td>
</tr>
<tr>
<td>RSA4</td>
<td>0.5801</td>
<td>0.1991</td>
<td>3.478</td>
</tr>
<tr>
<td>RSA5</td>
<td>0.9191</td>
<td>0.8099</td>
<td>2.549</td>
</tr>
<tr>
<td>RSA6</td>
<td>1.1451</td>
<td>0.7687</td>
<td>3.995</td>
</tr>
<tr>
<td>RSA7</td>
<td>1.3488</td>
<td>0.9404</td>
<td>1.967</td>
</tr>
<tr>
<td>RSA8</td>
<td>1.5014</td>
<td>0.8001</td>
<td>4.078</td>
</tr>
<tr>
<td>RSA.meanCV</td>
<td>0.6574</td>
<td>0.7832</td>
<td>1.669</td>
</tr>
<tr>
<td>RSA.meanCV$^2$</td>
<td>0.9847</td>
<td>0.9870</td>
<td>0.6001</td>
</tr>
</tbody>
</table>

**Conclusion:** RSA.meanCV$^2$ appears an optimal matrix in terms of accuracy (slope ~ 1) and precision (lowest residual error) amongst all RSAs considered. Same conclusion was derived for scenarios with 10%, 15%, 20%, and 25% TR differences.
Classification of PQRI CI Scenarios using RSA.mean.CV²
**Classification of PQRI 55 CI Scenarios Using Stepwise CI Equivalence Test**

RSA: RSA.mean.CV²

<table>
<thead>
<tr>
<th>Acceptance limit</th>
<th>% Agreement with PQRI Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>58</td>
</tr>
<tr>
<td>15%</td>
<td>65</td>
</tr>
<tr>
<td>20%</td>
<td>71</td>
</tr>
<tr>
<td>25%</td>
<td>75</td>
</tr>
<tr>
<td>30%</td>
<td>65</td>
</tr>
</tbody>
</table>
## Conclusions

<table>
<thead>
<tr>
<th>Open Questions (March 2013)</th>
<th>Current Knowledge (March 2014)</th>
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<tr>
<td>Determination of cut-off value for APSD equivalence testing</td>
<td>Yet to be determined</td>
</tr>
<tr>
<td>Construction of confidence intervals for MmCSRS (One-sided vs. two-sided)</td>
<td>Yet to be determined – minor issue</td>
</tr>
<tr>
<td>Influence of inter-site correlation structure on MmCSRS</td>
<td>Artefact of simulation approach</td>
</tr>
<tr>
<td>Best metric for reference variance scaling?</td>
<td>Has been determined</td>
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THANK YOU FOR YOUR ATTENTION