Content Uniformity Acceptance Testing for Large Sample Sizes: Nonparametric Counting Test

Kim Vukovinsky
Pfizer
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Presentation Outline

• ICH UDU and Translating Quality Requirements to Large n
• Large n Counting Test
  – 2006 to 2009 proposal
  – 2010 modified proposal
• Comments on # Tablets outside 75 – 125%
• Summary
ICH UDU TEST
THE QUALITY STANDARD
ICH UDU (2007+)

In 2007, the EP, JP, USP harmonized UDU test came into effect.

- Based on old JP test (two-sided tolerance interval)

- Indifference window arranged to achieve ~constant coverage for means within ~94 – 106%

- Multiplication factors 2.4 and 2.0 equate to 84% confidence of 91% within 85 – 115%. This was not specifically calculated at the time.

\[
\begin{align*}
\text{AV} = |\bar{X} - M| + 2.4S \\
M = \begin{cases} 
98.5, & \text{if } \bar{X} < 98.5 \\
\bar{X}, & \text{otherwise} \\
101.5, & \text{if } \bar{X} > 101.5 
\end{cases}
\end{align*}
\]
Interpretation of the OC Curve

The OC curve summarizes the test’s performance providing the probability of passing the requirement given a coverage (assuming data is normally distributed.)

A lot with 96% of its tablets between 85 – 115% LC has about a 65% chance of passing ICH UDU.
What is Coverage?

A calculation based on both the batch mean and the standard deviation of the process (i.e., manufacturing and assay)

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std Dev</th>
<th>RSD</th>
<th>% Tablets &gt;115</th>
<th>% Tablets &lt;85%</th>
<th>Coverage = % of tablets within 85 - 115%</th>
<th>Coverage = % of tablets within 75 - 125%</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>4.0</td>
<td>4.0</td>
<td>0.01</td>
<td>0.01</td>
<td>99.98</td>
<td>100.0000</td>
</tr>
<tr>
<td>100</td>
<td>5.0</td>
<td>5.0</td>
<td>0.13</td>
<td>0.13</td>
<td>99.73</td>
<td>99.9999</td>
</tr>
<tr>
<td>100</td>
<td>6.9</td>
<td>6.9</td>
<td>1.50</td>
<td>1.50</td>
<td>97.0</td>
<td>99.9703</td>
</tr>
<tr>
<td>98</td>
<td>6.6</td>
<td>6.8</td>
<td>0.51</td>
<td>2.48</td>
<td>97.0</td>
<td>99.9721</td>
</tr>
<tr>
<td>96</td>
<td>5.8</td>
<td>6.1</td>
<td>0.05</td>
<td>2.94</td>
<td>97.0</td>
<td>99.9846</td>
</tr>
<tr>
<td>94</td>
<td>4.8</td>
<td>5.1</td>
<td>0.00</td>
<td>3.04</td>
<td>97.0</td>
<td>99.9962</td>
</tr>
</tbody>
</table>
LARGE N LOT RELEASE
Large N: The Issue and Considerations

2003 Issue:
• With PAT, n is no longer 10/30 ... a new test is required.
• How are the current quality requirements translated to large n?
• What is the appropriate acceptance test and acceptance criteria?

Considerations:
• What is the quality standard?
• Is the current quality standard acceptable?
• How to match the quality standard?
• How will the test be used?
PhRMA PAT, Quality, and Statistics Team members met with the FDA (July 2004) to Determine Test Boundaries

- Quality Standard is USP 905 (now ICH UDU)
- Test should be Simple
- No Normality Assumption
- Match the ICH UDU at Probability of Acceptance = 50%
  (4.8% OOS at match point)
Matching Quality
Match Point of 10%, 50%, 90% corresponds to Coverage of 88.1%, 94.7%, 98.1% for 100% LC.
A maximal coverage of 95.17% (95.2%) is attained for a mean of 96.24% (96%) LC.

In large n test development, coverage of 95.2% was used.

The acceptance probability of a batch with 95% coverage of 85-115% LC is (for any mean) the same or tighter than the ICH-UDU test.
Large N Test: Three Options Considered

Parametric Tolerance Interval
- Analyze \( n \) dosage units.
- Express each individual result in % of label claim.
- Calculate the average and standard deviation.
- Look in Table for a \( k \)-value.
- Calculate statistic and determine lot status.
- Too complicated … issues with testing for normality.

<table>
<thead>
<tr>
<th>( n )</th>
<th>( LC )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100%</td>
<td>( k_1 )</td>
</tr>
<tr>
<td>500</td>
<td>100%</td>
<td>( k_2 )</td>
</tr>
<tr>
<td>100</td>
<td>96%</td>
<td>( k_3 )</td>
</tr>
<tr>
<td>500</td>
<td>96%</td>
<td>( k_4 )</td>
</tr>
</tbody>
</table>

Distribution Free Tolerance Interval
- Collect data for \( n \) dosage units; normalize to % label claim.
- Order sample \( x_{(1)} , \ldots , x_{(n)} \).
- Tolerance interval (TI) = \((x_{(L)}, x_{(U)})\); where \( L \) & \( U \) are determined by binomial probabilities (and depend on \( n \)).
- Accept batch if \( TI \subseteq (85, 115) \).
- Cool idea … very very complicated.

<table>
<thead>
<tr>
<th>Coverage (%)</th>
<th>Sample size (n)</th>
<th>Order statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>87.5</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>90.0</td>
<td>200</td>
<td>6</td>
</tr>
<tr>
<td>91.5</td>
<td>300</td>
<td>9</td>
</tr>
<tr>
<td>91.75</td>
<td>400</td>
<td>12</td>
</tr>
<tr>
<td>92.25</td>
<td>500</td>
<td>14</td>
</tr>
</tbody>
</table>

Nonparametric Counting Test
Large N Counting Test

- One tiered counting test
- Test translates to finding the largest integer \( t \), called \( c \), such that:

\[
c = \max\{t \mid \text{Prob}(Y \leq t \mid p = 0.048) \leq 0.5\}.
\]

\[
c = \text{round}(-1.15+0.048\times n)
\]
Large N OC curves are strictly to the left of the harmonized UDU test OC curve at the 50% pass line.
Quality requirements tighten as the mean is off target.

Large N Test (n=250, p=4.8%, 50% match) vs ICH UDU (μ=100 %LC)
Mixed Response to Matching at 50%

Negative: Some disagreement over having an area above the ICH UDU; Increased sample size creates increased probability to pass the test (depends on how quality is defined)

Positive: Accepted as a step forward to gaining process understanding and developing an acceptable test
MODIFIED LARGE N LOT RELEASE
Modified Large N

- Two proposals evaluated:
  - Matching at 90%
  - Maintaining a constant 3% of units outside 85 – 115%

- Number of tablets outside 75 – 125% considered
90% matching point for \( \mu = 100\% \)

The test translates to finding the largest integer \( t \), called \( c \), such that:

\[
c = \max\{t ; \text{Prob}(Y \leq t || p = 0.02) \leq 0.9\}.
\]

50% \( P(\text{accept}) \) std dev is 6.8 to 7.2% for \( n=100 \) to 500 vs. 7.7 for ICH UDU

\( c \) is 3, 7, 13 for \( n=100, 250, 500 \).
3% Outside 85 – 115% for μ = 100%

Set Quality Level (QL) = 1 – coverage (e.g. 3%)

\[ C = \text{Floor}(p \times N), \text{ where } p = \text{proportion of } N \text{ outside } [85, 115] \]

=> Same proportion used for all N.

50% P(a) std dev is 6.9 to 7.2% for n=100 to 500 vs. 7.7 for ICH UDU

c is 3, 7, 15 for n=100, 250, 500.
Large N Criterion: $\leq 3\%$ Outside 85-115\% LC


<table>
<thead>
<tr>
<th>Test</th>
<th>Sample Size</th>
<th>Acceptance Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH UDU</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>ICH UDU</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Large N</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Large N</td>
<td>250</td>
<td>7</td>
</tr>
<tr>
<td>Large N</td>
<td>500</td>
<td>15</td>
</tr>
</tbody>
</table>
Assuming normality ... the 3% counting test provides tighter control of the proportion of results outside 75-125%. A batch with 0.3% units outside 75-125% has about 25% chance to pass the ICH-UDU test, while the chance to pass the Large N 3% test is 5% for n=100 and approaches 0% for larger n.
Large N Criterion:
None Specified for 75-125% LC

- Batch acceptance should depend on quality level, not sample size
- Zero tolerance for tablets outside 75-125% LC is not advisable

# of batches Until 1 Tablet Found Outside 75 – 125% for a Mean of 100% LC and Std Dev of 5.0%
Advantages of Modified Counting Test

- Simple Test Mathematically
- Simple to Implement (no look up table required)
- Testing for Normality NOT Required
- Quality Level Consistent with the ICH UDU
- Increase in Sample Size Leads to a Tightened Quality Level

Large N Counting controls number of tablets outside 75 – 125% to a tighter level than ICH UDU even with no control on # outside 75 – 125%

Zero Tolerance of Tablets Outside 75 – 125% is not advisable; Sliding scale on quality level suggested
Acknowledgements

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- Joep Timmermans, Pfizer: Large N
- Jim Bergum, BMS: Modified Large N