Content Uniformity Acceptance Testing for Large Sample Sizes

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James Bergum, Bristol-Myers Squibb
May 25, 2011
Presentation Outline

• ICH UDU and Translating Quality Requirements to Large n
• Overview of Large n Counting Test
  – 2006 to 2009 proposal
  – 2010 modified proposal
• Comments on # Tablets outside 75 – 125%
• Summary
• Questions for Audience
USP <905> Uniformity of Dosage Units

Definition: The degree of uniformity in the amount of the drug substance among dosage units.
UDU - Demonstrating & Assuring Control

Process Development
- ICH Q8, Q9, Q10, Q11

Process Validation
- Agree on Quality Level (Clinical Relevance)
  - CuDAL
  - SPC
  - Weight/Other Control

Lot Release
- CuDAL
- By Process Control; No formal test
- Large N Lot Release
- PTIT, PTOSTI

Assure Quality on Market
- Quality Standard: ICH UDU
- Modify Standard: PTIT, PTOSTI
ICH UDU TEST

THE QUALITY STANDARD
Content Uniformity Test, USP <905>

<2007, two part acceptance criteria:
– # units outside a pre-defined range
– RSD

![Diagram](image-url)
ICH UDU (2007+)

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

- Based on old JP test.
- Based on a 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.
Interpretation of the OC Curve

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

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

• It is a summary statistic
• It is 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>
Harmonized ICH UDU

![Graphs showing probability of passing vs. coverage for different batches and regions.](image-url)
LARGE N LOT RELEASE
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 Parameters

- 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)
Large N Test: Where to Match ICH UDU?

Matching Quality
The coverage corresponding to a 10%, 50%, 90% probability of accepting the lot is 88.07%, 94.68%, 98.1%.
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 (TBD) 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>1.902</td>
</tr>
<tr>
<td>500</td>
<td>100%</td>
<td>1.943</td>
</tr>
<tr>
<td>100</td>
<td>96%</td>
<td>2.836</td>
</tr>
<tr>
<td>500</td>
<td>96%</td>
<td>2.873</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></td>
<td></td>
<td>Lower</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

- Paper Published
- One tiered counting test
- Test translates to finding the largest integer \( t \), called \( c \), such that:
  
  \[
  c = \max\{t \mid \text{Prob}(Y \leq t \mid p = 0.048) \leq 0.5\}.
  \]

\[
\begin{array}{c|cccccccc}
  n & 100 & 250 & 500 & 750 & 1000 & 2000 & 3000 & 4000 \\
c & 4 & 11 & 23 & 35 & 47 & 95 & 143 & 191 \\
\end{array}
\]

\[
c = \text{round}(-1.15 + 0.048 \times n)
\]
Large N Counting Test Performance

Batch Mean at 100% LC; Std Dev ~ 7.6% at match

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)
Advantages of Large N

- Simple Test Mathematically
- Simple to Implement (no look up table required)
- No Normality Assumption Required
- Quality More discriminating than ICH UDU
Mixed Response to Matching at 50%

Negatives

– Increased sample size creates increased probability to pass the test (many disagree as this depends on how quality is defined)

Positives

– Accepted as a step forward to gaining process understanding and developing an acceptable test
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
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 $\mu = 100\%$

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: ≤ 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>
Modified Large N Test Performance, n=250

- p=3% (Match with ICH UDU is >= 90%)

Large N Test (n=250) vs ICH UDU (µ=100% LC)

For a mean of 98 – 102%, need sd to be <5.5%
3% Large N Criterion Protects Against Results Outside 75-125% LC

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 acceptable

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

![Graph showing number of batches until one tablet found outside 75-125% LC for a mean of 100% LC and standard deviation of 5.0%](image)
Summary

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 acceptable; at minimum will need Table with Acceptance increasing with Sample Size (1 allowed out at 200)
Acknowledgements

- Fasheng Li, Pfizer: Graphics and Discussion
- Sonja Sekulic, Pfizer: Motivation and Discussion
- Dennis Sandell, S5 Consulting: Large N
- Myron Diener, sanofi-aventis: Large N
- Jeff Hofer, Eli Lilly: Large N
- Jim Pazdan, Novartis: Large N
- Joep Timmermans, Pfizer: Large N
Questions for the Audience

• Do you feel that tablet potency is normally distributed? What distribution do you expect the data will follow and why?
• Should we test for normality if using a normal based test?
• Do you feel that the release test needs to be simple?
• What is the benefit of Large N lot release?