Statistical Considerations for Establishing Acceptance Criteria for Content Uniformity and Stratified Sampling

Alex Viehmann
PQRI
06 October 2015
Disclaimer

This presentation is not official Agency policy. My statements and advice do not bind or otherwise obligate or commit the agency to the views expressed.
Agenda

- Sampling Methods
- Distribution considerations
- Quality levels – producer / consumer risk
- USP <905> - what does it provide?
- Acceptance criteria design
Sampling Methods

- **Simple Random Sampling**
  - Randomly pick units from lot

- **Stratified Sampling**
  - Divide Lot into strata where the combined strata cover the entire lot
  - Use random sampling within each strata.

- **Systematic Sampling**
  - Sample at specified points usually equally spaced throughout the lot.

- **Random vs. Stratified/Systematic**
  - Random = no estimation of between/within location variability
Comparison of Sampling Methods
Distribution considerations

- What is the underlying distribution?
  - Probability plot
  - Normality test

Note: Statistical tests are sensitive to high sample sizes.
Parametric vs Distribution-free

- **Parametric**: Assume the data follow a specific distribution
  - Example: Not enough evidence to conclude the distribution is non-normal
- **Distribution-free**: Do not assume the data follow a specific distribution
- Parametric tests can perform well with skewed and non-normal distributions and when the spread of each group is different
  - Follow sample size guidelines
- Limited knowledge/data to confirm distribution or severely skewed distributions (best represented by median) = distribution-free techniques
Quality Levels

**Acceptable**: The quality level that would be accepted with a high probability (e.g. 95%)  
Producers risk

**Unacceptable**: The quality level that would be rejected with a high probability (e.g. 90%)  
Consumers risk

21 CFR 210.3(20): .... Acceptance criteria means product specifications and acceptance criteria, such as **acceptable quality level and unacceptable quality level**, with an associated sampling plan....
USP <905> GC for demonstrating Uniformity of Dosage Units

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number tested</th>
<th>Pass stage if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>S₁</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S₂</td>
<td>20</td>
<td>i)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) No dosage unit is outside the maximum allowed range of 0.75<em>M to 1.25</em>M.</td>
</tr>
</tbody>
</table>

M is defined as follows:
- If T is less than or equal to 101.5%LC, and
  - i) If X is less than 98.5%LC, then M = 98.5%LC.
  - ii) If X is between 98.5 and 101.5%LC, then M = X.
  - iii) If X is greater than 101.5%LC, then M = 101.5%LC.
- If T is greater than 101.5%LC, and
  - i) If X is less than 98.5%LC, then M = 98.5%LC.
  - ii) If X is between 98.5 and T, then M = X.
  - iii) If X is greater than T, then M = T.

T is the Target content per dosage unit at the time of manufacture, expressed as percentage label claim. Unless otherwise specified in the individual monograph, T is 100.0%LC.
USP <905> background

- The procedure is based on a two-sided tolerance interval approach.
  - An interval that contains p percent of the population measurements
    - N=10 / k₂=2.4
    - N=30 / k₂=2.0
      - k₂ is a tolerance interval factor that is affected by sample size, desired confidence, and coverage (k₂ is specific to a two sided tolerance interval)
      - K₂ is determined so that the interval covers at least a proportion p of the population with a confidence c

- Based upon the criteria of the test (k₂ value), the metrics provided are – 84% confident that 91% of the population lies between +/- 15%

- The second aspect of the procedure is no tablet will be outside ~ 73.9-126.9%
USP <905> - Acceptance Region / OC curve
Blend Uniformity

• Draft guidance acceptance criteria was inconsistent with current Agency thinking
  – Old recommendation: sample multiple units (replicates) from multiple locations (e.g. 3 samples from 10 locations) and only assay 1 per location = total of 10 measurements
    • Mean (90-110%) / SD < 5%
  – Level II Q/A recommendation: assay all replicates
    • Allow for estimation of between/within location variance components

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm
Variance Components

• Partitions total variability into its individual sources of variation

• Examples:
  – Between/within locations
  – Between/within batches
Designing appropriate acceptance criteria

- What is the sampling method?
  - Random, stratified or systematic

- What is the underlying distribution?

- What are the quality levels that are required for this product/process?
Example I

- Sampling Method = Systematic
- Data = Continuous / Normal
  - Sample size = 60 (15x4)
- Assurance requirements = 90% confident that at least 95% of samples will meet USP standard
  - Coverage = true proportion of samples from the batch that will meet USP <905>
- Method = ASTM E2709 / 2810; sampling plan 2
<table>
<thead>
<tr>
<th>Location</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97.08</td>
<td>99.72</td>
<td>98.37</td>
<td>97.50</td>
</tr>
<tr>
<td>2</td>
<td>99.72</td>
<td>100.32</td>
<td>101.01</td>
<td>100.29</td>
</tr>
<tr>
<td>3</td>
<td>99.90</td>
<td>98.27</td>
<td>98.88</td>
<td>97.96</td>
</tr>
<tr>
<td>4</td>
<td>98.78</td>
<td>98.17</td>
<td>98.94</td>
<td>97.78</td>
</tr>
<tr>
<td>5</td>
<td>96.32</td>
<td>96.61</td>
<td>99.66</td>
<td>97.20</td>
</tr>
<tr>
<td>6</td>
<td>100.97</td>
<td>102.17</td>
<td>99.06</td>
<td>98.80</td>
</tr>
<tr>
<td>7</td>
<td>97.02</td>
<td>97.35</td>
<td>98.65</td>
<td>99.98</td>
</tr>
<tr>
<td>8</td>
<td>99.39</td>
<td>98.81</td>
<td>98.63</td>
<td>98.06</td>
</tr>
<tr>
<td>9</td>
<td>99.59</td>
<td>97.80</td>
<td>97.67</td>
<td>98.95</td>
</tr>
<tr>
<td>10</td>
<td>97.97</td>
<td>98.54</td>
<td>100.26</td>
<td>98.74</td>
</tr>
<tr>
<td>11</td>
<td>96.09</td>
<td>98.61</td>
<td>97.49</td>
<td>97.50</td>
</tr>
<tr>
<td>12</td>
<td>98.87</td>
<td>97.81</td>
<td>97.28</td>
<td>98.80</td>
</tr>
<tr>
<td>13</td>
<td>101.10</td>
<td>102.60</td>
<td>100.48</td>
<td>98.62</td>
</tr>
<tr>
<td>14</td>
<td>100.80</td>
<td>100.34</td>
<td>98.49</td>
<td>100.93</td>
</tr>
<tr>
<td>15</td>
<td>99.70</td>
<td>100.09</td>
<td>100.14</td>
<td>99.20</td>
</tr>
</tbody>
</table>
Example: Sampling Plan 2

Data vs. Location

CU (%LC) vs. Location

Location: 1 to 15

CU (%LC) range from 90 to 110
### Example: Sampling Plan 2

#### Descriptive Statistics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mean</td>
<td>98.93</td>
</tr>
<tr>
<td>SE (within-location Std Dev)</td>
<td>1.07</td>
</tr>
<tr>
<td>Standard deviation of Location Means</td>
<td>1.06</td>
</tr>
</tbody>
</table>

#### 90%CI/95%Cov

<table>
<thead>
<tr>
<th>SE</th>
<th>0.9</th>
<th>1.0</th>
<th>1.1</th>
<th>1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LL</td>
<td>UL</td>
<td>LL</td>
<td>UL</td>
</tr>
<tr>
<td>0.9</td>
<td>88.1</td>
<td>111.9</td>
<td>88.5</td>
<td>111.5</td>
</tr>
<tr>
<td>1.0</td>
<td>88.2</td>
<td>111.8</td>
<td>88.6</td>
<td>111.4</td>
</tr>
<tr>
<td>1.1</td>
<td>88.4</td>
<td>111.6</td>
<td>88.7</td>
<td>111.3</td>
</tr>
<tr>
<td>1.2</td>
<td>88.5</td>
<td>111.5</td>
<td>88.9</td>
<td>111.1</td>
</tr>
<tr>
<td>1.3</td>
<td>88.7</td>
<td>111.3</td>
<td>89.0</td>
<td>111.0</td>
</tr>
</tbody>
</table>
Example II

- Sampling Method = Random
- Data = Distribution unknown; attribute data
  - Attribute: 85-115% LC
- Assurance requirements = 90% confident that at least 98% batch will be in spec.
  - Coverage = true proportion of batch within desired spec
- Method = Attribute sampling plan
Example II: OC curve

AQL = 0.25% (95% probability the lot will be accepted if % defective ≤ 0.25%)
UQL = 2% (90% probability the lot will be rejected if % defective ≥ 2%)
Example III

- Sampling Method = Random
- Data = Continuous / Normal
  - Spec: 90-110%
- Sample size = 60
- Assurance requirements = 95% confident that at least 95% batch will be in spec.
  - Coverage = true proportion of batch within desired spec
    - NMT 2.5% below 90%; NMT 2.5% above 110
- Method = Two one-sided Tolerance Interval test
Example III acceptance criteria

- $X_{\text{bar}} + (2.38 \times s) < 110$
- $X_{\text{bar}} - (2.38 \times s) > 90$

$2.38$ = one-sided tolerance interval factor representing $95\%$ confidence, $97.5\%$ coverage and sample size=$60$
Summary

• Sampling method needs to be defined
  – Dictates the ability to quantitate between/within variance components

• Distribution needs to be evaluated
  – Dictates the method to apply

• Attribute (spec range) needs to be relevant for the product
  – Is 85-115% appropriate for all drug products?

• Quality levels = Risk Based
  – Should not be static across all products

• Firm needs to clearly identify the assurance the plan provides
  – OC curve