Sampling Considerations for UDU Release Testing in Continuous Manufacturing
• Since continuous manufacturing permits flexible batch sizes, a variable number of batch samples for release testing are possible.

• In this presentation, four sampling plans for release testing of Uniformity of Dosage Units (UDU) are discussed. These plans can accommodate variable sample sizes.

• These four UDU release criteria will be discussed and compared against the USP <905> criteria.
Depicting Possible Batch Sampling in Continuous Manufacturing

- Sampling frequency examples:
  - By time: sampling every 10 minutes
  - By mass: sampling every 10K units
- When equal samples are taken at each time location ("L"), the sample sizes per batch ("n") are different.
Simulation Assumptions for Plan Evaluation

<table>
<thead>
<tr>
<th>Simulation Parameters</th>
<th>Batch Manufacturing Time (Hours)</th>
<th>Number of Batch Locations</th>
<th>Sample Size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch Mean*</td>
<td>100.0 and 96.0 %LC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch Standard Deviation</td>
<td>From 0 to 10 %LC, with 0.2 %LC increments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Variability Explained by Batch Location*</td>
<td>0 and 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampling Frequency</td>
<td>3 units every 10 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replicates/case</td>
<td>5,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** * Due to presentation space constraints, only OC curves for the extremes batch mean and batch location variance percentages combinations are provided.
USP <905> UDU Test

• USP <905> test is a compendial criteria used to ensure that every dosage unit contains the amount of drug substance intended with little variation within a batch.

• This is a two stage test that requires:
  – Evaluating 10 dosage units at stage 1, and 30 dosage units at stage 2 (including the initial sample of 10 units).
  – That an acceptance value (AV) criteria in either stage falls within 15.0%, with: AV=|M – mean|+k (s), where:
    • “k” equals 2.4 at stage 1, and equals 2.0 at stage 2
    • “M” = Min{ Max( 98.5, mean),105.5} for target ≤101.5
  – That no dosage unit deviates from the calculated value M by more than 25% of M at stage 2.
USP <905> UDU Test (cont.)

Let: Stage=1 and k = 2.4. Obtain 10 content uniformity tests.

Calculate the sample mean and std. dev. from the n results.

Let Stage=2 and k=2.0. Obtain 20 additional content uniformity tests, for a total n=30.

Assuming that target content per unit dosage \( \leq 101.5\% \text{ LC} \), calculate “M”, such as:
- M= mean when 98.5\% \leq \text{ mean} \leq 101.5\%
- M=98.5\% when \text{ mean} < 98.5\%
- M=101.5\% when \text{ mean} > 101.5\%

Calculate acceptance value (AV) as:
\[ AV = |M - \text{ mean}| + k*\text{(std. dev.)} \]

AV \( \leq 15.0 \)?

Stage=1?

Yes

Stage=1?

Any result > (25\% of M)?

Yes

Pass

No

Fail

Yes

No
UDU Release Testing Alternatives: Modified Large N Test

• In this modified version of the Large N Test:
  – A sample of size n is taken and the number of individuals falling outside 85.0 to 115.0 %LC is counted.
  – The test passes if the count is less or equal to an acceptance number “c”.
  – Finds “c” by matching the USP<905> test at a 90% probability of passing. The original version of the test* matches the USP<905> test at a 50% probability of passing and is less stringent than this modified version.
  – Could be applied when the batch sample size is greater or equal to 100, because the discrete nature of the test more severely impacts the pass rates with smaller sample sizes.

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UDU Release Testing Alternatives: Modified Large N Test (Cont.)

<table>
<thead>
<tr>
<th>Large N Test Version</th>
<th>Probability (&quot;Pr&quot;) of Passing USP &lt;905&gt; UDU Test</th>
<th>% Individuals within 85.0 to 115.0 %LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>Pr=0.50 (50% matching point)</td>
<td>95.2% (→ p = 0.048)</td>
</tr>
<tr>
<td>Modified</td>
<td>Pr=0.90 (90% matching point)</td>
<td>98.0% (→ p = 0.02)</td>
</tr>
</tbody>
</table>

\[
c = \text{Max} \left\{ x \mid \sum_{i=0}^{x} \binom{n}{i} \cdot p^i \cdot (1 - p)^{n-i} \leq Pr \right\}
\]
UDU Release Testing Alternatives: Modified Large N Test (Cont.)

- OC curves for this modified Large N test exhibited marginal differences from the USP<905> test at high probability levels, due to: (i) the 90% matching point, and (ii) the effect of sample size on the OC curve slopes.

- But these differences are exacerbated with offsets in the batch means and with increases in location-to-location variability.
UDU Release Testing Alternatives: One-Tiered Plan

- When the batch sample size is between 15 and 100, a one-tiered UDU Plan could be employed calculating an acceptance value with multiplier “k” which varies with the sample size.

- This is: $AV = |M - \text{mean}| + k \cdot (s)$, with:
  
  “M” calculated as specified in USP<905>  

\[
k = \begin{cases} 
2 + \left(\frac{\theta}{2} \cdot \frac{n - 30}{15}\right), & \text{for } 15 \leq n < 30 \\
2 + \left(\theta \cdot \frac{n - 30}{70}\right), & \text{for } 30 \leq n < 100 \\
N/A & \text{for } n < 15 
\end{cases}
\]

Where “θ” is a tuning parameter that controls the stringency of “k”
UDU Release Testing Alternatives: One-Tiered Plan (Cont.)

- To pass this one-tiered test:
  - $AV \leq 15.0$
  - No dosage unit deviates from the calculated value $M$ by more than 25% of $M$.

- For our assessment, k’s tuning parameter “$\theta$” was set to 0.15 because it yielded OC curves with a comparable level of stringency with respect to the USP<905> test.
  - If stringent OC curves are required, $\theta > 0.15$. 

OC curves for this One-Tiered plan exhibited marginal differences from the USP<905> test at both high and low probability levels, due to the effect of sample size on the OC curve slopes. 

- When n>30, plan OC curves started to drop a little bit later.
- When n<30, plan OC curves started to drop a little bit early.
UDU Release Testing Alternatives: CUDAL (ASTM E2709/E2810) Sampling Plan

- CUDAL stands for “Content Uniformity and Dissolution Acceptance Limits” and the use of these limits has been proposed on the ASTM standards E2709 and E2810.
- The assurance of the method is achieved by:
  - Calculating a confidence region on the average and standard deviation estimated from the UDU sample.
  - The extremes of this confidence region are compared to a lower bound probability of passing USP <905>.
  - If the confidence region is within the lower bound, then there is the appropriate confidence of passing the test.
UDU Release Testing Alternatives: CUDAL (ASTM E2709/E2810) Sampling Plan (Cont.)

• Lower Bound probability calculations are described by Bergum and Li.
• The confidence region used were developed by Lindgren and are described in ASTM standard E2810.


UDU Release Testing Alternatives: CUDAL (ASTM E2709/E2810) Sampling Plan (Cont.)

- For implementation purposes, the CUDAL SAS Program Ver. 2.0 is available, and generates the table below. (This program was written by James Bergum and validated through PhRMA’s statistical expert team).
- For a given mean, the table provides the maximum acceptable “CV” (i.e., coefficient of variation). If calculated sample CV ≤ Acceptance CV in the table, the acceptance criteria is met.

<table>
<thead>
<tr>
<th>MEAN (% CLAIM)</th>
<th>CV (%)</th>
<th>MEAN (% CLAIM)</th>
<th>CV (%)</th>
<th>MEAN (% CLAIM)</th>
<th>CV (%)</th>
<th>MEAN (% CLAIM)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.1</td>
<td>0.48</td>
<td>90.1</td>
<td>1.37</td>
<td>95.1</td>
<td>3.11</td>
<td>100.1</td>
<td>4.16</td>
</tr>
<tr>
<td>85.2</td>
<td>0.51</td>
<td>90.2</td>
<td>1.39</td>
<td>95.2</td>
<td>3.13</td>
<td>100.2</td>
<td>4.13</td>
</tr>
<tr>
<td>85.3</td>
<td>0.54</td>
<td>90.3</td>
<td>1.92</td>
<td>95.3</td>
<td>3.16</td>
<td>100.3</td>
<td>4.10</td>
</tr>
<tr>
<td>85.4</td>
<td>0.57</td>
<td>90.4</td>
<td>1.94</td>
<td>95.4</td>
<td>3.18</td>
<td>100.4</td>
<td>4.07</td>
</tr>
<tr>
<td>89.7</td>
<td>1.76</td>
<td>94.7</td>
<td>3.01</td>
<td>99.7</td>
<td>4.12</td>
<td>104.7</td>
<td>2.87</td>
</tr>
<tr>
<td>89.8</td>
<td>1.79</td>
<td>94.8</td>
<td>3.03</td>
<td>99.8</td>
<td>4.14</td>
<td>104.8</td>
<td>2.84</td>
</tr>
<tr>
<td>89.9</td>
<td>1.81</td>
<td>94.9</td>
<td>3.06</td>
<td>99.9</td>
<td>4.16</td>
<td>104.9</td>
<td>2.82</td>
</tr>
<tr>
<td>90.0</td>
<td>1.84</td>
<td>95.0</td>
<td>3.08</td>
<td>100.0</td>
<td>4.18</td>
<td>105.0</td>
<td>2.79</td>
</tr>
</tbody>
</table>

ACCEPTANCE LIMITS FOR CONTENT UNIFORMITY (N= 30, TARGET = 100.0) SAMPLING PLAN 1
(MEETING LIMITS GUARANTEES, WITH 95.0% ASSURANCE, THAT AT LEAST 95.0% OF SAMPLES Tested FOR CONTENT UNIFORMITY WILL PASS THE USP TEST)
• CUDAL 95/95 is substantially more conservative than the USP<905> in either condition tested.
UDU Release Testing Alternatives: CUDAL (ASTM E2709/E2810) Sampling Plan (Cont.)

- OC curves for CUDAL 50/50 get closer to USP<905> when $n \geq 60$, with some differences in larger sample sizes.
UDU Release Testing Alternatives: CUDAL (ASTM E2709/E2810) Sampling Plan (Cont.)

- The observed differences observed with CUDAL 50/50 could be addressed by moving the plan towards the left (either adjusting the confidence or the lower bound probability).
  - As an example of the configurability of the plan, the OC curves for CUDAL 50/95 are provided below.
UDU Release Testing Alternatives: Normal Tolerance Limits Based Sampling Plan

• This plan requires that two-sided normal tolerance intervals of the UDU results fall within the 85.0% to 115.0% LC.

• These normal tolerance limits (NTL) are computed as follows:

\[
NTL = \text{mean} \pm \left( K_{1-\alpha/2,p,n} \right) (S)
\]

Where “\( K_{1-\alpha/2,p,n} \)” is a normal tolerance interval multiplier such that, with a sample size of “\( n \)” is able to provide a “1-\( \alpha/2 \)” confidence of covering at least a proportion “\( p \)” of the population.
UDU Release Testing Alternatives: Normal Tolerance Limits Based Sampling Plan (Cont.)

- The Normal Tolerance Interval based plans could be configured, as shown in the plot for n=30.
- The table below summarizes the configuration results across the various n’s.
  - Multiplier adjustments were done to get a plan that performs similar to the USP<905> under a given condition (e.g.: a particular mean and location variability % scenario).

<table>
<thead>
<tr>
<th>n</th>
<th>K(95/97.5)</th>
<th>K(95/96.25)</th>
<th>K(95/95)</th>
<th>K(95/93.75)</th>
<th>K(95/92.5)</th>
<th>K(95/90)</th>
<th>K(95/87.5)</th>
<th>K(95/85)</th>
<th>K(95/82.5)</th>
<th>K(95/80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>3.238</td>
<td>3.006</td>
<td>2.832</td>
<td>2.691</td>
<td>2.572</td>
<td>2.376</td>
<td>2.216</td>
<td>2.080</td>
<td>1.960</td>
<td>1.852</td>
</tr>
<tr>
<td>30</td>
<td>2.923</td>
<td>2.713</td>
<td>2.556</td>
<td>2.429</td>
<td>2.322</td>
<td>2.145</td>
<td>2.000</td>
<td>1.877</td>
<td>1.769</td>
<td>1.671</td>
</tr>
<tr>
<td>60</td>
<td>2.670</td>
<td>2.479</td>
<td>2.335</td>
<td>2.219</td>
<td>2.121</td>
<td>1.960</td>
<td>1.828</td>
<td>1.715</td>
<td>1.616</td>
<td>1.527</td>
</tr>
<tr>
<td>90</td>
<td>2.575</td>
<td>2.390</td>
<td>2.252</td>
<td>2.140</td>
<td>2.046</td>
<td>1.890</td>
<td>1.763</td>
<td>1.654</td>
<td>1.558</td>
<td>1.472</td>
</tr>
<tr>
<td>120</td>
<td>2.522</td>
<td>2.341</td>
<td>2.206</td>
<td>2.096</td>
<td>2.004</td>
<td>1.851</td>
<td>1.727</td>
<td>1.620</td>
<td>1.526</td>
<td>1.442</td>
</tr>
<tr>
<td>216</td>
<td>2.442</td>
<td>2.266</td>
<td>2.135</td>
<td>2.029</td>
<td>1.940</td>
<td>1.792</td>
<td>1.671</td>
<td>1.568</td>
<td>1.478</td>
<td>1.396</td>
</tr>
<tr>
<td>432</td>
<td>2.378</td>
<td>2.207</td>
<td>2.079</td>
<td>1.976</td>
<td>1.889</td>
<td>1.745</td>
<td>1.628</td>
<td>1.527</td>
<td>1.439</td>
<td>1.360</td>
</tr>
</tbody>
</table>
UDU Release Testing Alternatives: Normal Tolerance Limits Based Sampling Plan (Cont.)

- OC curves for the normal tolerance interval based plan exhibited marginal differences from the USP<905> test when batches were on target, due to the effect of sample size on the OC curve slopes.
- When batches were off-target and $n \geq 30$, Tolerance interval based plans were more stringent than the USP<905> test because these do not include an indifference zone around the mean.
The implementation of this plan may require the use of a table lookup of the multipliers.

– But it may be possible to interpolate multiplier data to estimate a “K” for a sample size, when sufficient (not too dispersed) multiplier data are available.
Concluding Remarks

• The various plans may be employed in a flexible batch setting for UDU release testing, as they could have similar or higher stringency in probability of passing than USP <905>.

• Some characteristics of the plans:
  – The level of stringency for the plans could be adjusted.
  – Only the Normal Tolerance Interval based plan could be used virtually across any sample size range.
  – The implementation of these plans may require a table lookup and intermediate criteria assessment calculations.