Discussion:
MANUFACTURING: New Developments in Uniformity Test

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Acknowledgements

- MANUFACTURING: New Developments in Uniformity Test
- Organizer/Chair: Yuanyuan Duan and Lanju Zhang, AbbVie

- Lanju Zhang: A hypothesis test perspective on content uniformity test
- Meiyu Shen: Large sample dose content uniformity test: parametric versus nonparametric (counting)
- Jeff Hofer: Analysis and visualization approaches to assess UDU capacity
- Xiaoyu (Cassie) Dong: Quality assurance test of delivered dose uniformity of multiple-dose inhaler and dry powder inhaler drug products
A Hypothesis Test Perspective on Content Uniformity Test

Lanju Zhang

Data and Statistical Sciences AbbVie Inc
What is the type I error of the PT-TOST when the batch is on the $H_0/H_1$ border?

$H_0/H_1$ border

Exactly 6.25% of individuals in the batch are < 85% LC and/or

Exactly 6.25% of individuals in the batch are > 115% LC

$\mu - Z_p \sigma = 85\%$ and/or $\mu + Z_p \sigma = 115\%$
Scenario 1: $\mu = 110$, $\sigma = 3.26$

$\text{Prob pass} = 0.05$
Scenario 2: $\mu = 100, \sigma = 9.78$

Prob pass $< 0.01$
The PT-TOST does have correct significance level (=0.05).

A batch like scenario 1 (6.25% outside of 85-115) is better than scenario 2 (12.5% outside of 85-115).
Improvements to PT-TOST

Lanju proposes the “MLE” test
This is a two-sided test, not two one-sided tests.

Test statistic: $|\bar{X} - T| + Z_p s$

Rejection region: $|\bar{X} - T| + Z_p s < C$

The value $C$ is determined by Monte Carlo methods

Are the test properties better than PT-TOST?

Use Bayesian methods to directly test: $|\mu - T| + Z_p \sigma < 15$
Extensions to PT-TOST

Lanju proposes extending the PT-TOST test

Control the mean:
PT-TOST and $| \mu - T | < 10$

Control the standard deviation:
PT-TOST and $\sigma < 6$

Can perform with Bayesian methods + vague prior
Large sample dose content uniformity test: parametric and nonparametric (counting)

Meiyu Shen, PhD
Collaborators: Xiaoyu Dong, Ph.D., Yi Tsong, PhD
Office of Biostatistics, CDER, FDA

* This presentation contains opinions of the authors that do not represent the official position of U.S. Food and Drug Administration
Content uniformity testing when $n \geq 100$

EU gives two options
- Parametric two-sided tolerance interval test
- Non-parametric counting test

Meiyu proposal (PTIT_matchUSP90)
- Parametric two one-sided tolerance interval test

Both TI tests are constructed as $85 < \bar{X} \pm K s < 115$

For normally distributed data,
- EU value for $K$ is based on asymptotics
- PTIT_matchUSP90 value for $K$ is exact
- As $n \to \infty$, the two values for $K$ agree.
Normal: on target product, mean=100%
Analysis and Visualization Approaches to Assess UDU Capability

Presented at MBSW 2015
19 May 2015
Jeff Hofer, Adam Rauk
Establishes content uniformity for single dosage units.

Two-tier testing with \( n_1 = 10, \ n_1 + n_2 = 30 \).

Assume Target \( T = 100 \),

\[
M = \begin{cases} \bar{X} & \text{if } 98.5 < \bar{X} < 102.5 \\ 98.5 & \text{if } \bar{X} < 98.5 \\ 102.5 & \text{if } \bar{X} > 102.5 \end{cases}
\]

Let \( AV_i = |M - \bar{X}| + K_i s \) \((K_1 = 2.4, K_2 = 2.0)\)

Tier 1: \( AV_1 < 15\% \)

Tier 2: \( AV_1 > 15\%, AV_2 < 15\%, \) and \( 0.75M < X_i < 1.25M \)
ASTM E2810

a.k.a., CuDAL method

Provides confidence that random samples from the same batch would meet USP<905> criteria.

Various ASTM E2810 sampling plans
  Sample batch locations and units within location

Jeff/Adam propose visualization of ASTM E2810
  • Bayesian methods to draw from posterior distribution of Mean, SD[between], SD[within] to create conservative credible interval for CuDAL acceptance probability.
95% Pass Contours for Mean=100 & Credible Intervals for Line Segment Creation
Two extensions

   • Given enough batches, one can also produce posterior distribution of batch-to-batch variability.
   • Calculate predictive posterior *probability that future batches will meet ASTM E2810*.

   • Better optimality for confidence region for \((\mu, \sigma)\).
Quality Assurance Test of Delivered Dose Uniformity of Multiple-dose Inhaler and Dry Powder Inhaler Drug Products

Yi Tsong¹, Xiaoyu (Cassie) Dong*¹, Meiyu Shen ¹ & Richard T. Lostritto ²

¹: Office of Biostatistics/Office of Translational Sciences, CDER, FDA
²: Office of Pharmaceutical Sciences, CDER, FDA

*This article reflects the views of the authors and should not be construed to represent FDA’s views or policies
USP<601> DDU Test

Tier 1, 10 containers (10 beginning, 10 end)

- At most 2 of 20 $\notin$ (80%, 120%)
- All 20 $\in$ (75%, 125%)
- Average of each 10 $\in$ (85%, 115%)

Yes $\rightarrow$ Complies

No $\rightarrow$ Tier 2, additional 20 containers (20 beginning, 20 end)

- At most 6 of 60 $\notin$ (80%, 120%)
- All 60 $\in$ (75%, 125%)
- Average of each 10 $\in$ (85%, 115%)

Yes $\rightarrow$ Complies

No $\rightarrow$ Not complies
TOSTI - Product Quality Definition

- Most lot (>P%) within (80%, 120%)

- Not much (< (1-p)/2%) outside each end of (80%, 120%)

- **WITH 95% CONFIDENCE**

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Two-sided Hypotheses

\[ H_0 : \Pr(L < X < U) \leq P \]
\[ H_1 : \Pr(L < X < U) > P \]

Two One-sided Hypotheses

\[ H_0 : \Pr(X < L) \geq \frac{1-P}{2} \text{ or } \Pr(X > U) \geq \frac{1-P}{2} \]
\[ H_1 : \Pr(X < L) < \frac{1-P}{2} \text{ and } \Pr(X > U) < \frac{1-P}{2} \]
Two One-sided Tolerance Intervals Procedure (TOSTI)

<table>
<thead>
<tr>
<th>Test Attribute</th>
<th>Current Practice</th>
<th>TOSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean limit</strong></td>
<td>85-115% of LC</td>
<td>85-115% of LC</td>
</tr>
<tr>
<td><strong>Individual limits</strong></td>
<td>None allowed outside 75-125%</td>
<td>No limit on individuals</td>
</tr>
<tr>
<td><strong># of tiers</strong></td>
<td>2 tiers with a 1:3 ratio of sample sizes</td>
<td>2 tiers with a 1:3 ratio of sample sizes</td>
</tr>
<tr>
<td><strong>Tier sample size</strong></td>
<td>Guidance defined “Inflexible”</td>
<td>Applicant defined “Flexible”</td>
</tr>
<tr>
<td><strong>Tier II testing versus Tier-I</strong></td>
<td>Less likely to pass at Tier-II (individual limit effect)</td>
<td>More likely to pass at Tier-II (design feature of the test)</td>
</tr>
</tbody>
</table>

Two one-sided PTIT for DDU

FDA-proposed test
• Single tier
• \( n = \) total sample size (beginning + end)

\[ 80 < \bar{X} \pm K \frac{s}{\sqrt{n}} < 120 \]

where \( K = T^{-1}(0.95, df = n-1, ncp = \Phi((1+ p)/2)\sqrt{n})/\sqrt{n} \)
Draw a line in the sand.

Consider a normal distribution for $X$ with $\mu = 100$. Choose a true coverage and acceptance probability.

Then there exists $\sigma = \sigma_0$ such that

$$\Pr( 80 < X < 120 ) = \text{coverage}$$

For any sample size $n$, there exists $p$ such that

$$\Pr( \text{Accept batch} \mid \mu=100, \sigma=\sigma_0 ) = \text{acceptance probability}$$
FDA large sample DDU proposal (my example)

Constants

$\mu = 100$
Coverage = 96.3%  
(same as $\sigma = 9.58$
$\alpha = 0.05$
Acceptance Prob=0.7

For new $n$, find $p$
Same coverage
Same acceptance prob

$n=20/20$: $p=0.844$
$n=30/30$: $p=0.875$
$n=150/150$: $p=0.933$
Tolerance interval coverage linked to $n$

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>$p$</th>
<th>Coverage Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=20/20</td>
<td>0.844</td>
<td>95%/84.4% TI</td>
</tr>
<tr>
<td>n=30/30</td>
<td>0.875</td>
<td>95%/87.5% TI</td>
</tr>
<tr>
<td>n=150/150</td>
<td>0.933</td>
<td>95%/93.3% TI</td>
</tr>
</tbody>
</table>

Traditional Testing: Set $\alpha=0.05$ and $p=0.875$,
- Statistical power is a function of sample size
- Test size = $\alpha$ whenever $\mu +/- \sigma Z_p = 80$ or 120
- Hypothesis testing is well-understood

FDA proposal:
- Different $100(1-\alpha)%/100p%$ TI for each sample size
- Is hypothesis testing well-understood?
Thank you to all the speakers and organizers!