Content Uniformity (CU) testing for the 21st Century: CDER Perspective

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Outline

• Introduction
• USP <905>
  – Summary
  – Features
• Case study 1: Levothyroxin
• Case study 2: Split Tablets
• Alternatives to USP <905>
• Parametric Tolerance Interval Testing (PTIT)
• Case study 3: PTIT
• Summary and conclusions
Introduction: Setting the Stage

• Content Uniformity (CU) testing is an important assessment of unit dosage form performance.
• Because pharmacological responses are dynamic, variable, and their manifestations easily confounded, clinical response alone cannot serve as an arbiter of adequate CU performance.
• CU testing is usually destructive and consumes resources (wet chemical analyses)
Introduction: Setting the Stage

• In some cases CU testing may not be destructive
  – e.g., Near Infrared (NIR) and weight variation (WV)
• Process Analytical Technologies (PAT) and Real Time Release Testing (RTRT) allow for more frequent and convenient sampling
  – Greater product knowledge
  – More efficient use of resources / less off line analysis
  – High assurance of product quality
Introduction: Launch point

- Is USP <905> perfect? No.
- Is USP <905> adequate? Not all the time.
- What are the weaknesses in USP <905>?
- Are there viable alternatives?
  - Parametric Tolerance Interval (PTIT)
  - Large N
- Cases of interest
  - Narrow therapeutic index drugs
  - Drug device combination products
  - Specialized dosage forms (e.g., inhalation)
Summary of USP<905>

• Applies to many dosage forms
• Weight variation (WV) versus content uniformity (CU) for tablets (as an example)
  – If < 25 mg or < 25% then CU
  – If > 25 mg and > 25% then WV
• Sample sizes for tablets are
  – 10 units (L1) and
  – 30 units (L2 as L1 + 20 more)
Summary of USP<905> (as CU for tablets)

• Acceptance value, $AV = |M-X| + ks$
  – $X = \text{sample mean as percent of label claim (}\%\text{LC})$
  – $K = 2.4$ for L1 and $K = 2.0$ for L2
  – $S = \text{standard deviation of the SAMPLE}$
  – $M$ depends on the sample mean
    • If $X$ is between $98.5 \%\text{LC}$ and $101.5 \%\text{LC}$ then $M = X$
    • If $X$ is $< 98.5 \%\text{LC}$ then $M = 98.5$
    • If $X$ is $> 101.5 \%\text{LC}$ then $M = 101.5$
    • This scenario creates a zone of indifference to the mean
  – $AV$ cannot exceed $15.0$ at L1 or $25.0$ at L2

• There are also limits on individual values
Summary of USP<905> (as CU for tablets)

- Limits on individual values in L2
  - No unit < 0.75 M and
  - No unit > 1.25 M
  - That means no unit outside 75 -125 %LC for on target mean (if the mean is within 1.5% of LC)
  - For off target means (> ±1.5%) the limits on individuals vary
Features of USP <905> as CU for tablets

- Fixed sample sizes as L1 and L2 (10 / 30)
- L1 (especially) and L2 are relatively small and may not provide for a confident estimation of the batch compared to larger sample sizes.
- There are limits on individual values.
  - Is that valid in a statistically relevant model?
- There is a 1.5% zone of indifference around 100%LC.
  - Rewards off-target sample mean
  - Also changes M which changes individual limits
Case Study 1: Levothyroxine

• Potency
  – Drug product specifications allow up to 10% loss of potency over expiry
  – Intermediate strengths (112-150 mcg) are separated by less than 10% of dose.
  – One strength has degraded to contain less active than a lower strength tablet.

• Tighter controls necessary for potency to assure accuracy of individualized dosing which is titrated per patient.
Case Study 1: Levothyroxine

- CU
  - Variability is also observed within batch
  - Loss of potency and inter batch variability are linked
    - Both affect content uniformity performance
  - Using USP <905> at L1 (10 tablets) for low dose case
    - With 10% loss of potency an RSD ≤ 2.7% passes
    - With 5% loss of potency an RSD ≤ 4.8% passes
    - For reference, at 100% LC, an RSD ≤ 6.25% passes
    - USP <905> has a zone of indifference of 1.5% ± LC
  - Meeting USP <905> content uniformity with < 5% potency loss may provide reasonable assurance that strengths do not lose order of potency on stability.
Case Study 2: Split Tablets

- Economic driving forces encourage tablet splitting
  - Typically, the 2X strength product is not doubly expensive
  - Patients, prescribers, and insurers recognize this
- Current practices for immediate release tablets
  - Splitting of scored and non scored tablets
  - Hand splitting
  - Kitchen knives and other household implements
  - Tablet splitters (not regulated)
Case Study 2: Split Tablets

• What are some potential problems?
  – If scored, is the score functional?
    • Ease to split (splitability)
    • Even splitting by weight
    • Loss of mass (crumbs) typically 1-2%
  – Performance of the major pieces (i.e., halves) regarding:
    • Friability
    • Dissolution rate
    • Physical and chemical stability
    • Content uniformity (esp low dose cases)
Case Study 2: Split Tablets

• Some Points to Consider for CU of the pieces
  – Which tablets are appropriate for splitting (IR vs. ER)?
  – Is a functional score necessary?
  – Valid assessment of “splitability”?
  – Stability assessment (90 days post dispensing?)
    • New active surface exposed
    • New sharp edges and corners exposed
  – Dissolution assessment (meet same specifications?)
  – Loss of mass (what’s a maximum allowable loss?)
  – Content Uniformity
    • Should each piece Meet USP <905>?
Potential Alternatives to USP <905>

• Large N
  – For RTRT approaches, FDA has approved Large N approaches using WV and NIR
  – May be appropriate when large numbers of tablets can be adequately measured; usually non destructively
    • The Agency is working with a goal to develop harmonized criteria with other regions for Large N approaches

• Parametric Tolerance Interval Testing (PTIT)
  – Similar to some Large N approaches, but typically smaller sample sizes
  – Discussed in FDA Draft Guidance (add reference)
Parametric Tolerance Interval Testing (PTIT)

- **What is PTIT?**
  - A statistically relevant way of estimating CU by measuring it in a sample

- **The test has two sample tiers Tier-1 and Tier-2**
  - A different concept than L1 and L2 of USP<905>
  - Applicant chooses and specifies the tier sizes based on confidence in their process and product performance.

- **Let’s explore further through an example**
  - Case 3
Parametric Tolerance Interval Testing (PTIT)

- What are the advantages of PTIT over USP<905>
  - Sample size choices are more flexible
  - Sample sizes (2 tiers); typically larger than USP but smaller than “Large N”
  - Passing at Tier-1 rewards high quality
  - No zone of indifference
  - No restriction on individual values
    - No zero tolerance
PTIT: BATCH Distributions, Goalposts, and the Concept of COVERAGE.
Parametric Tolerance Interval Testing (PTIT)

- If the mean is >100 %LC, \( \text{MSD} = \frac{[120 - \text{SM}]}{K} \)
- If the mean is < 100 %LC, \( \text{MSD} = \frac{[\text{SM} - 80]}{K} \)

Where
- \( \text{SM} = \text{sample mean} \)
- \( \text{MSD} = \text{the maximum sample standard deviation allowable to PASS at this Tier (1 or 2)} \)
- \( K \) is a PTI model derived constant and depends upon
  - Sample size
  - Tier-I or Tier-II
  - Relationship to Tier-I to Tier-II
  - The goalposts
  - The desired coverage between the goalposts
Parametric Tolerance Interval Testing (PTIT)

• Note that:
  – The smaller K is, the larger the allowable MSD is
  – The closer Sample Mean (SM) is to 100% of target, the larger is the allowable MSD
  – The smaller the sample SD is, the more off-target SM may be and still pass the test
  – SM must be within the goalposts (obvious)
  – There is no model constraint on individual values

• Here are some values of K…
# PTIT K values

<table>
<thead>
<tr>
<th>% coverage</th>
<th>N=10</th>
<th>N=30</th>
<th>N=20</th>
<th>N=60</th>
<th>N=30</th>
<th>N=90</th>
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<tbody>
<tr>
<td>Tier-I</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tier-II</td>
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<td></td>
</tr>
<tr>
<td>K10</td>
<td>2.82</td>
<td>1.94</td>
<td>2.20</td>
<td>1.74</td>
<td>2.00</td>
<td>1.66</td>
</tr>
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<td>K30</td>
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<td>K20</td>
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<tr>
<td>K30</td>
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<td>2.16</td>
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<td>2.23</td>
<td>1.86</td>
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<tr>
<td>K90</td>
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<tr>
<td>N = sample size</td>
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</tbody>
</table>
Case 3: Simulated Batch for PTIT

• Design a sim batch
  – Let batch mean = 100 %LC
  – Let batch Sd = 8.0 %
• Let Goalposts be 80% to 120% of LC
• Set coverage to 90% within goalposts
• Try the smallest possible sampling plan
  – Tier-I = 10
    • MSD = [SM-80]/K10 or MSD = [120-SM]/K10
  – Tier-II = 30
    • MSD = [SM-80]/K30 or MSD = [120-SM]/K30
• Select appropriate K values from the Table
### Case 3: Simulated Batch for PTIT

<table>
<thead>
<tr>
<th>% coverage</th>
<th>(N=10)</th>
<th>(N=30)</th>
<th>(N=20)</th>
<th>(N=60)</th>
<th>(N=30)</th>
<th>(N=90)</th>
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<tbody>
<tr>
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<td>82.5</td>
<td>2.82</td>
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<td>2.00</td>
<td>1.66</td>
</tr>
<tr>
<td>Tier-II</td>
<td>85.0</td>
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</tr>
<tr>
<td></td>
<td>90.0</td>
<td>3.31</td>
<td>2.60</td>
<td>2.07</td>
<td>2.37</td>
<td>1.98</td>
</tr>
</tbody>
</table>

\(N=\) sample size

<table>
<thead>
<tr>
<th>(K)</th>
<th>(K10)</th>
<th>(K30)</th>
<th>(K20)</th>
<th>(K60)</th>
<th>(K30)</th>
<th>(K90)</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>82.5</td>
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Case 3: Simulated Batch for PTIT

- Tier-I = 10
  - MSD = [SM-80]/3.31 or MSD = [120-SM]/3.31
- Tier-II = 30
  - MSD = [SM-80]/2.30 or MSD = [120-SM]/2.30

- Pass if sample standard deviation < MSD
- Do that 30 times
- Here’s the results of the first 10 runs
Case 3. SM=100% and SD=8.0%
90% coverage using smallest sampling plan: 10 / 30

<table>
<thead>
<tr>
<th>Run #</th>
<th>N=10</th>
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<th>Tier-I</th>
<th>Tier-II</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SM</td>
<td>SD</td>
<td>SM</td>
<td>SD</td>
</tr>
<tr>
<td>1</td>
<td>100.5</td>
<td>10.7</td>
<td>99.5</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>98.9</td>
<td>7.1</td>
<td>98.0</td>
<td>7.8</td>
</tr>
<tr>
<td>3</td>
<td>98.3</td>
<td>9.5</td>
<td>100.4</td>
<td>8.8</td>
</tr>
<tr>
<td>4</td>
<td>100.6</td>
<td>5.9</td>
<td>101.9</td>
<td>6.3</td>
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<tr>
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<td>8.7</td>
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<tr>
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<td>100.2</td>
<td>8.6</td>
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Case 3: Simulated Batch for PTIT

• Undesirable outcome
  – The batch passed only 21/30 times
  – There were no Tier-I passes

• Explaining this outcome
  – Goalposts too far apart?
  – Coverage too high?
    • Increase coverage -> larger K
  – Sample sizes too small ?
    • Decrease sample size -> larger K

• Let’s try larger sample tier sizes
  – Larger samples are more likely to represent the batch
  – The requirements for larger samples are less stringent
Case 3: Simulated Batch for PTIT

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</table>

N = sample size
Case 3. Sm=100% and SD=8.0%
90% coverage using LARGEST sampling plan: 30 / 90

- $K_{30} = 2.37$
- $K_{90} = 1.98$
- Run sampling and testing 30 times
- Results
  - Pass Tier-I about half the time
  - Pass Tier-II 29/30 times
Case 3. Sm=100% and SD=8.0%
90% coverage using LARGEST sampling plan: 30 / 90

• This may be an acceptable situation
  – Reasonable opportunity to pass at Tier-I
    • (good)
  – High probability to pass at Tier-II
    • (very good)
  – No limit on individuals
    • (excellent)
  – The applicant has the option to select and specify the sampling plan to suit their risk and resources
  – May be resource intensive at Tier-II
    • Typically, coverage is set at 90% between goalposts
Parametric Tolerance Interval Testing (PTIT)

- What are the issues with PTIT?
  - Technically assumes a normal distribution of the measured property in the batch. However, provided the distribution is symmetrical, it should be ok.
    - If CU variability is not random, look for, evaluate, and control for operative non-random causes
  - There are multiple PTIT approaches
    - Tier sizes and ratios
    - Various ways to weight the power of tiers
    - Various goalposts and coverage within goalposts
  - There is no universal agreement on best approach
    - However…
Parametric Tolerance Interval Testing (PTIT)

- The Agency has identified some PTIT approaches that may be acceptable for CU testing. For inhalation products these include:
  - Goalposts 80% to 100% of label claim.
  - Coverage within goalposts, 90% of batch population
  - Two sample size tiers in a 1:3 ratio
    - For example, 10:30, 20:60, 30:90, etc.
    - Power (as 1-alpha) equally distributed between tiers
    - The applicant chooses and specifies the tier sizes
  - Cases vary; **recommend discussion** with the Agency before implementing
Case Study 4: Drug Eluting Cardiac Stents

- Very low drug levels in or on the stent
- Potent drugs used (e.g., paclitaxel)
- Extended release design, in place a long time
- Local treatment of vulnerable target tissue
- Local tissue levels likely in therapeutic range.
  - Dose response relationships exist
- The vast majority of these products comply with USP <905> for tablets at L1 (n=10)
Summary and Conclusions

• In some cases USP <905> works fine for CU testing, but it has flaws:
  – Small fixed sample sizes for L1 and L2
  – Zone of indifference of 1.5%
  – Limits on individual values and they may vary according to the sample mean

• PTIT testing offers greater flexibility and appears to have greater statistical relevance provided the batch distribution is near-normal or symmetrical
Summary and Conclusions

- Loss of potency on stability for a narrow therapeutic drug may put more demands on what is acceptable CU performance.
- Split tablet performance is a current and pervasive issue that merits careful consideration in terms of CU.
- Pharmacokinetic and pharmacological input can further help to determine the criticality of CU performance to safety and efficacy.
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