Regulatory Update on Pharmaceutical Quality Statistics

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October 15th , 2014
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Agenda

- Enforcement Action Examples
- CGMP References
- ASTM Standards
- Acceptance Criteria
- Update on Powder Blends

Examples: Recent Warning Letters, Recalls, and 483 Citations

- WL: Incorrect application of sampling plans
- Recall: application of ASTM E2709
- UL: Blend Uniformity, Acceptance Criteria
- 483 Notice of Observations

1. Warning Letter – Sampling Plans

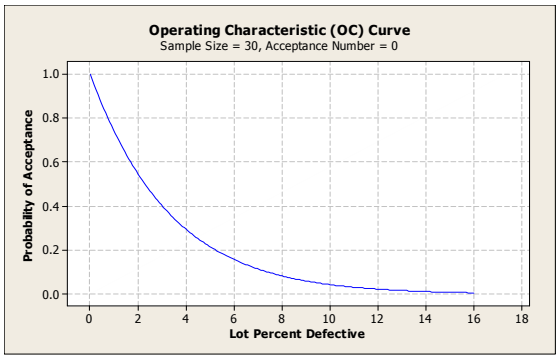
- Firm using sampling plans incorrectly
  - Pooled X vials, used only 1 reportable value, but used n=X in sampling plan.
  - *….based your lot or batch acceptance/rejection criteria on a single reportable value averaged from a pooled sample.*

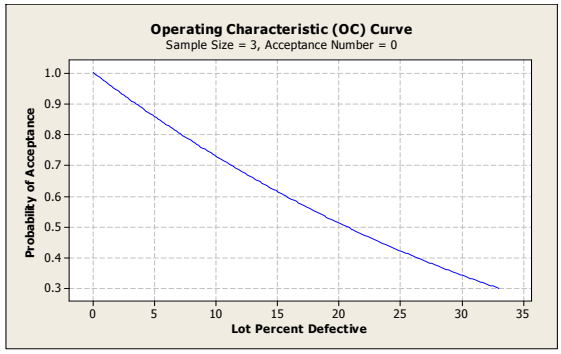
  …

  For ….., you are collecting 3 pooled samples (each pool = 10 vials). This equates to a lot disposition action on 3 reportable values with corresponding AQL of X% and LQ of X% respectively. This is not equivalent to an X or X plan as claimed in your SOP.

1. Warning Letter – Sampling Plans

- Response to 483 indicated firm did not know how to use and interpret sampling plans correctly.
- Firm did not understand concepts of Acceptable Quality Level (AQL) and Limiting Quality (LQ) and Operating Characteristic Curve (OC) of a specific sampling plan.





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Application of ASTM E2709 (Referenced in PV Guidance) - Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure.

Tablets, Q value: 70%

Background: Firm having recall issues due to dissolution failures on stability. Dissolution data analyzed using ASTM 2709. Sample data below shown for 2 lots (each row = different lot).

Take-home: ***If evaluated correctly, these lots would have been flagged as high risk for failure.***

Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6	Unit 7	Unit 8	Unit 9	Unit 10	Unit 11	Unit 12	Mean	SD	RSD	USP - PASS or FAIL	ASTM E2709 Probability @ 95% confidence
96%	72%	82%	74%	102 %	70%	97%	63%	71%	78%	74%	60%	**78%**	**14%**	**17%**	**Pass**	**0.14%**
77%	73%	90%	95%	92%	59%	73%	94%	60%	72%	62%	85%	**78%**	**13%**	**17%**	**Pass**	**0.14%**

Untitled Letter

- Firm discontinued Blend Uniformity Testing for Commercial without assurance of within batch or batch-to-batch drug uniformity
- Firms' response relied on parametric methods without distribution analysis
- Firms' response relied on process capability studies without establishing process control (using within estimate of sigma)
- Firm relying solely on USP compendial testing for lot release without demonstrating a capable or controlled process.

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Untitled Letter

- "Your firm failed to establish valid in-process specifications (21CFR 211.110(b))."
- "The firm failed to establish adequate acceptance criteria for the sampling and testing conducted by the quality control unit to assure that the batches of drug products meet each appropriate specification and appropriate statistical quality criteria as a condition for their approval and release (21 CFR 211.165(d))."

483 Notice of Observations

- SPC program deficiencies
- Assessed SPC SOP for established products
- Firm improperly deriving control limits
  - By using long term standard deviation
  - By limiting the standard deviation at a set P_{pk}
- Approach differs from established consensus standards and may not signal out of statistical control

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483 Notice of Observations

- Sampling plan deficiencies
  - "…SOP XX is inadequate because there is no documented scientific rationale for determining if the acceptance and rejection levels are appropriate for lot release…"
  - Firm failed to understand/characterize final quality statement from application of plans
  - CGMP requires credentialed personnel

CGMP References

- 211.110(a) & (b)
- 211.165(d)
- 211.180(e)
- Preamble for 21 CFR 210, 211

Key elements in these requirements

- Control procedures
- Monitor the output
- Performance
- Variability in the characteristics of in-process material and the drug product
- ….derived from previous acceptable process average and process variability estimates **(**where possible)
- ….determined by...suitable statistical procedures **(**where appropriate)

Statistics

- Can sample units at any stage of process and analyze for:
  - Weight.
  - Content Uniformity.
  - Dissolution.
  - Other critical quality attributes and or parameters of interest.
- Can make decisions at any stage of process with respect to:
  - Ability for a lot to pass USP UDU and or Dissolution tests in the future. (ASTM E2709)
  - Confidence in sampling. (ASTM E2334 & ASTM E122)
  - Capability and Performance analysis. (ASTM E2281)
  - Statistical Process Control Charts. (Monitor Variation, ASTM E2587)
- Following tools illustrate making inferences about untested units on a particular attribute, variable and or parameter with respect to sample size and an associated confidence.

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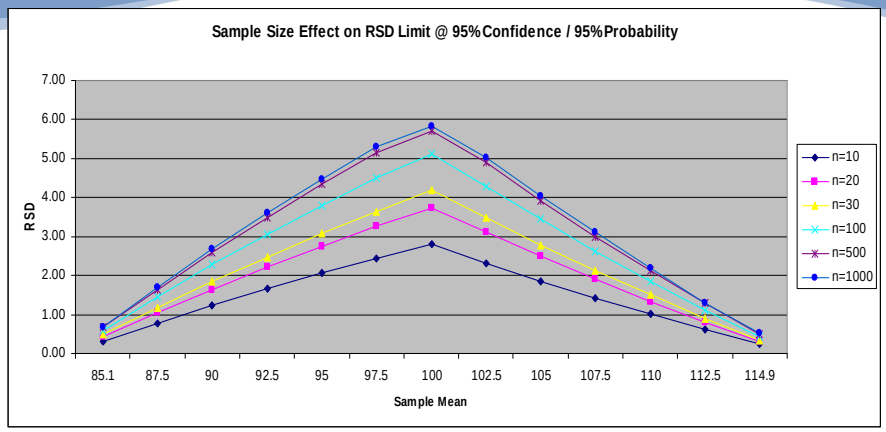
Voluntary Consensus Standards: US Government Agencies

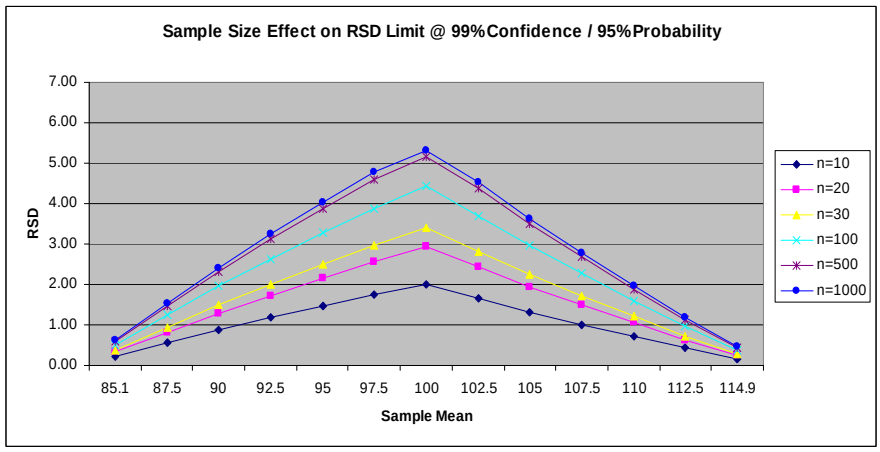
- OMB Circular A119
  - Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities (Rev. Feb 10, 1998)
  - directs agencies to use voluntary consensus standards in lieu of government-unique standards except where inconsistent with law or otherwise impractical
  - intended to reduce to a minimum the reliance by agencies on government-unique standards.

http://www.whitehouse.gov/omb/circulars/a119/a119.html

Demonstrating Statistical Confidence

Measurement by Variables





ASTM E2709
Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure

One tool to analyze Uniformity of Dosage Units

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ASTM E2709 Explanation

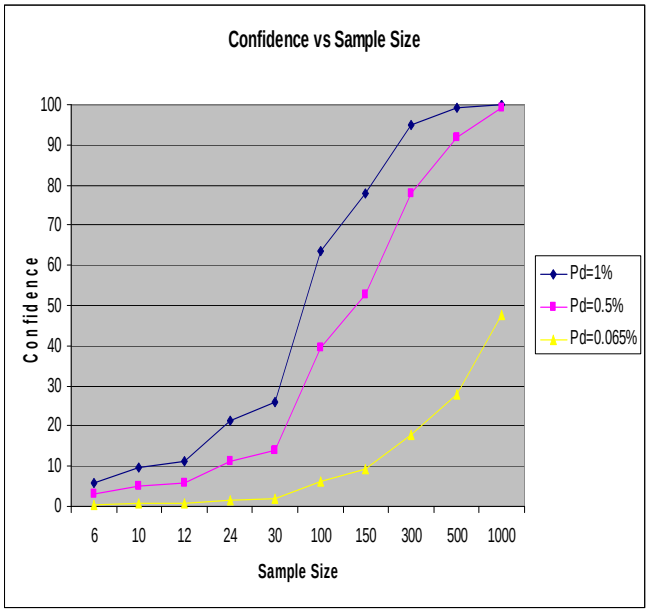
Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure

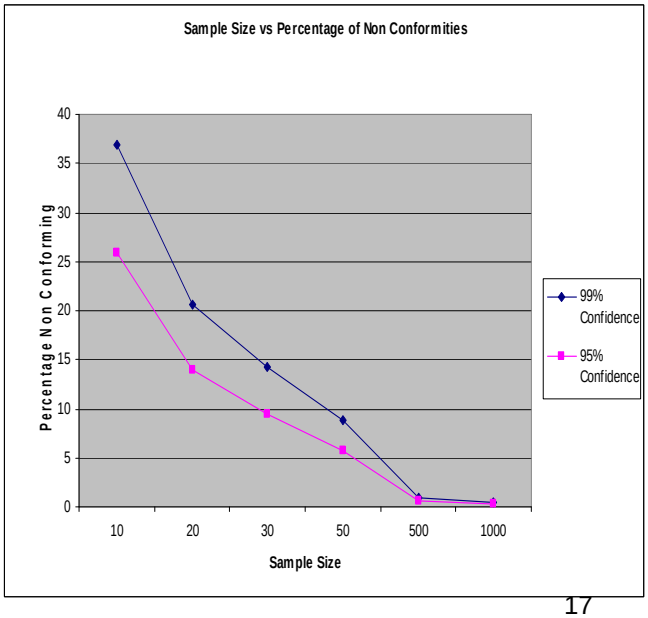
- Slide shows the relationship between sample size and tolerance for variability. As sample size increases, so does the tolerance for variability.
- The analysis was performed using ASTM E2709-10. The RSD limits on the y-axis represent the maximum variability a lot can possess to ensure with 95 or 99% confidence that there is at least a 95 or 99% probability a lot will comply with the USP Uniformity of Dosage Units test based upon a given sample size, confidence level, and sample mean.
  - For example: If you sampled 30 units and had a sample mean of 95%, then the maximum RSD value for those 30 units would be ~3.0% to be 95% confident that there is at least a 95% probability a future sample from the lot would pass the USP UDU test.

Demonstrating Confidence Measurement by Attributes

ASTM E2334

Setting an Upper Confidence Bound For a Fraction or Number of Non-Conforming items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When There is a Zero Response in the Sample





ASTM E2334 Explanation

Setting an Upper Confidence Bound For a Fraction or Number of Non-Conforming items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When There is a Zero Response in the Sample

- Slide shows the relationship between Confidence and Sample Size. As sample size increases, so does confidence demonstrated.
- The analysis was performed using ASTM E2334-09. Keeping the maximum percent defective constant (1, 0.5, and 0.065%) a line was generated to show how sample size effects the confidence demonstrated in having no more than the maximum percent defective. A zero response was assumed (that is zero defects in the sample) and a binomial distribution was used.
  - For example: If you desire a percent defective of no more than 0.5% and sample 30 units, then you are only ~15% confident that your lot has no more than 0.5% defects.

ASTM E2334 Explanation

Setting an Upper Confidence Bound For a Fraction or Number of Non-Conforming items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When There is a Zero Response in the Sample

- Slide shows the relationship between the upper confidence bound on percent defects and sample size. As sample size increases the upper confidence bound on percent defects decreases.
- The analysis was performed using ASTM E2334-09. Keeping the confidence level constant (95 and 99%) a line was generated to show how sample size effects the upper confidence bound percent defects. A zero response was assumed (that is zero defects in the sample) and a binomial distribution was used.
  - For example: If you want to be 99% confident that there is no more than 1% defective units in your lot, then you must sample ~460 units with a zero response.

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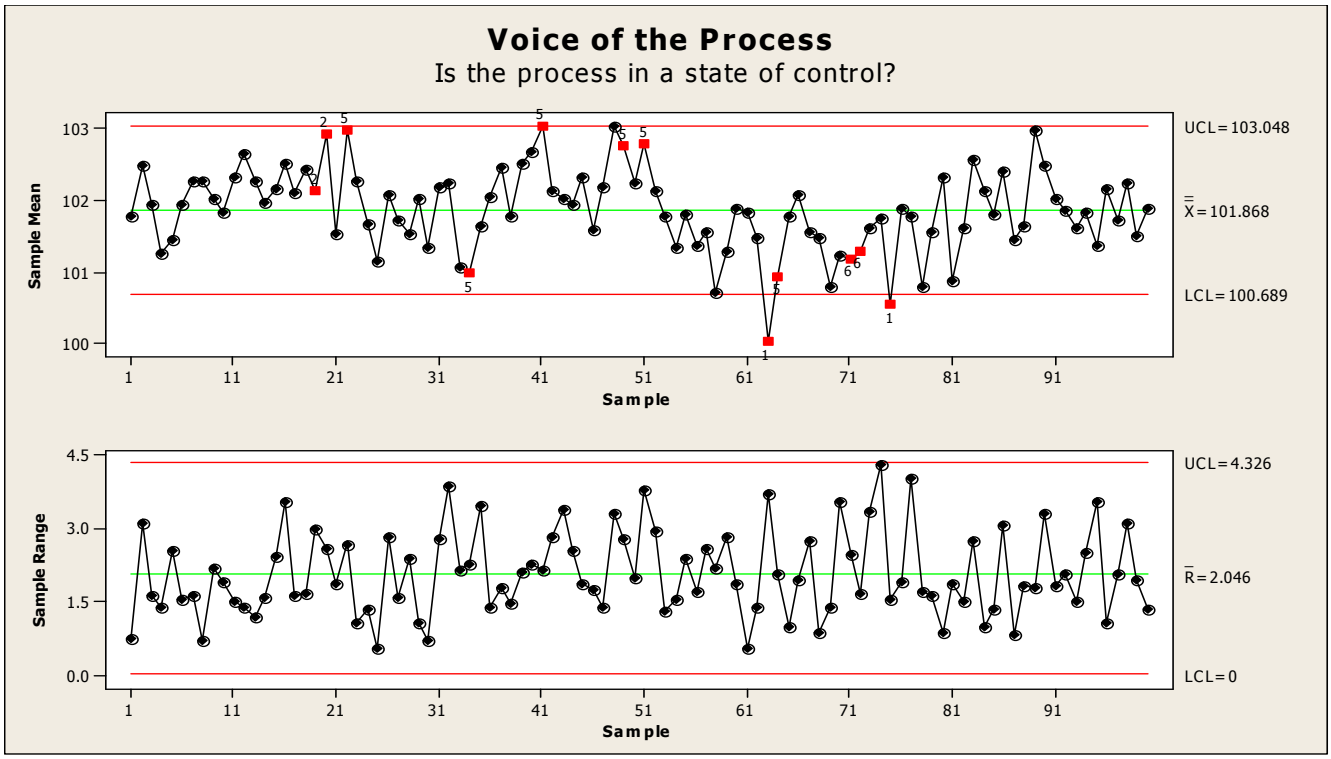
ASTM E2587

Standard Practice for Use of Control Charts in Statistical Process Control

- SPC (Statistical Process Control) Charts are a collection of very effective statistical-graphical tools which can be used to:
  - Understand and diagnose your data.
  - Track performance to identify problems, or shifts in performance (good or bad).
  - Control or adjust the process to maintain desired performance.
- Can be applied for data based on Incoming, In-process, or Lot release samples.
- Can be applied for both variable and attribute data.

ASTM E2587 Standard Practice for Use of Control Charts in Statistical Process Control

Variable X-bar-R chart



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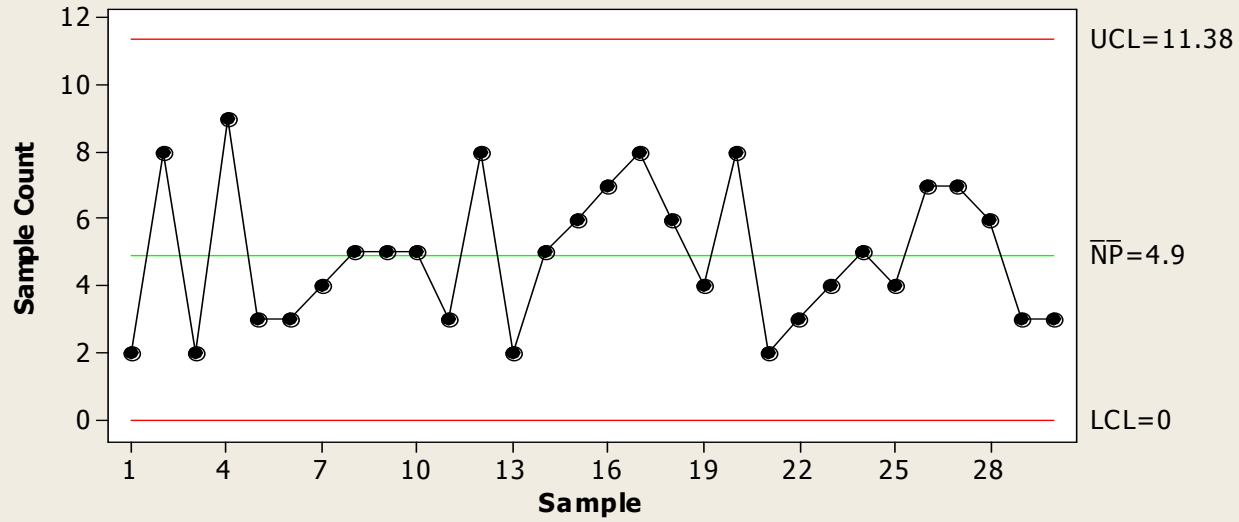
ASTM E2587

Standard Practice for Use of Control Charts in Statistical Process Control

- Chart is used to detect special causes of variation during manufacturing.
- Control is determined against standard 8 rules established by Dr. Walter Shewhart.
- Preceding chart is called X-bar-Range with Subgroup size of 5 tablets (each point is an average of 5 individual results).
- Control limits reveal true variability of the process.

ASTM E2587 Standard Practice for Use of Control Charts in Statistical Process Control

Attribute nP chart



Here we assume the failure rate is 5 bottles/100 bottles
Need to know historical defect rate from supplier

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SPC Checklist

- Points to Consider with SPC
  - Is the data normally distributed?
    - Possible use of a run chart for limited or non-normal data
    - Note: There may be SPC chart applications for non-normal data
  - What is the rational subgroup size?
  - What does the SOP say with respect to
    - How to Establish Control Limits?
    - How often are Control Limits Revised?
    - Which SPC rules to use?
    - What to do if a rule is violated?
    - Magnitude of change that is important?
    - Is a shift in mean or variance important or both?
    - What is the Average Run Length (ARL or false positives)?
      - If data is non-normal, it will increase SPC rule violations which may not necessarily be an indication of an out of control process.
    - How are the samples taken and do they follow a linear time sequence?
    - Are the samples independent?
- Relevant CGMP that can be used for SPC
  - 211.110, 211.160, 211.165

Establishing Acceptance Criteria

- What are the appropriate quality levels?
  - Acceptable / Unacceptable
- What is the distribution of my data?
  - Normal / Unknown / Not normal / etc.
- What is the risk of the product and/or attribute?
  - Are there controls in place to mitigate the risk?

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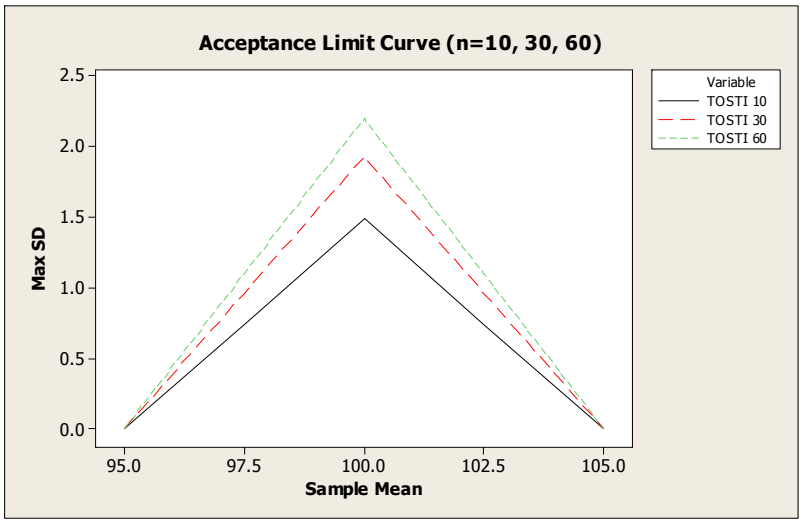
Example of Acceptance Criteria for Normally Distributed Data

- Attribute: Content Uniformity
- Limit: 95-105 %
- Data: Continuous / Normal
- Assurance Metric:
  - 95% confident / NMT 2.5% of population is below 95%
  - 95% confident / NMT 2.5% of population is above 105%
- Test: Two One Sided Tolerance Interval

Acceptance Limit Curve



Based on the above acceptance limit curves, the user will select the appropriate sample size based on (previous) acceptable process average and variability estimates.
Interpretation of curve:

Sample Size: 30
Sample Mean: 97.5
Acceptance: The SD on the 30 units must be less than or equal to 0.963.

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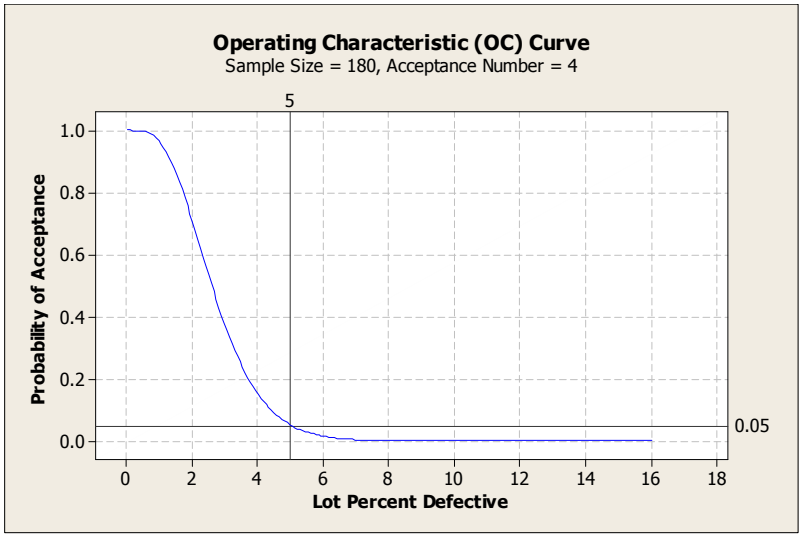
Example of Acceptance Criteria for Unknown or Non-Normal Data

- Attribute: Content Uniformity
- Limit: 95-105 %
- Assurance Metric:
  - 95% confident / NMT 5% of population is out of spec
- Test: Single Stage Attribute Sampling Plan

Operating Characteristic Curve



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Evaluation of Acceptance Criteria

- Controls for off-target means
- Controls for a proportion of the lot to be between the LSL and USL at a given confidence level
  - Potential defects are evenly distributed (i.e. equal potential defects below LSL and above USL)
- Establishes a quality level based on risk of product and attribute

Acceptance Criteria Example

- Information Request (IR) for an NDA
  - "Please amend all acceptance criteria to account for off-target sample means. The maximum standard deviation limit should not be static for the range of acceptable sample means and should decrease as the sample mean moves away from target (i.e. 100% LC). This will ensure appropriate confidence and coverage levels for the batch at any acceptable sample mean."

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Update on Powder Blends

- FDA issued notice of withdrawal for draft guidance on "Powder Blends and Finished Dosage Units- Stratified In-Process Dosage Unit Sampling and Assessment."
- Issued a Level II Q&A on fda.gov website
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm
  - Questions 15 - 18

Level II Q&A

Q 15 - Addresses FDA's major concerns with draft guidance

Q 16 – Concerns with proper sampling of powder blends

Q 17 – Recommended innovative approaches to ensure adequacy of mixing

Q 18 - Recommendations regarding in-process stratified sampling of finished dosage units

Acknowledgements

- Alex Viehmann – CDER/OPS
- Grace McNally – CDER/OC