Statistical Considerations for Review of Manufacturing Process

Karthik Iyer
Process Reviewer
Office of Process and Facilities
June 16th, 2016
Quality and Productivity Research Conference

* This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Outline

• Process Review
• Update on Powder Blends
• ASTM Standards
• Statistically Based Acceptance Criteria
• Conclusion
Areas of Focus in Process Review

• Process Review Areas
  1. Batch formula/commercial scale process flow diagram
  2. Rationale for selection of manufacturing process
  3. Adequacy of manufacturing process description

• Statistics used in the following Process review areas
  4. In-process controls, process parameter settings
  5. Scale up
  6. Microbiological control
  7. Comparability protocols
Use of Statistics

• Evaluation of proposed in-process controls and associated acceptance criteria

• Evaluation of Blend Uniformity
  – Homogeneity assessment

• Evaluation of Content Uniformity
  – large sample sizes

• Comparing adequacy of performance of Real Time Release Testing Method (for example, NIR vs. HPLC)
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• FDA issued notice of withdrawal for draft guidance on “Powder Blends and Finished Dosage Units- Stratified In-Process Dosage Unit Sampling and Assessment.”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
  – 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Q 15 - Addresses FDA’s major concerns with draft guidance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
Voluntary Consensus Standards:

• What are Standards?
  – ANSI, ASTM, ISO
  – Peer recognized and go through a critical review process by experts.

• OMB has directed federal use of voluntary consensus standards except where inconsistent with law or otherwise impractical. (OMB Circular A119)

• Use of Standards?
  – By Applicants to explain manufacturing data and set acceptance criteria
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
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.
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?
Other ASTM Standards

• ASTM E2281 – Standard Practice for Process and Measurement Capability Indices
• ASTM E122 – Standard Practice for Calculating Sample Size to Estimate, with Specified Precision, the Average for a Characteristic of a Lot or Process
• ASTM E2334 – Standard Practice for Setting and Upper Confidence Bound for 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 E2782 – Standard Guide for Measurement System Analysis
• ASTM E456 – Standard Terminology Relating to Quality and Statistics
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?
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
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.
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

Operating Characteristic (OC) Curve
Sample Size = 180, Acceptance Number = 4
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
Conclusion

• Assurance of consistent manufacture of desired product quality

• Regulators have been steadfast in encouraging industry to adopt science and risk based principles for manufacturing process development

• Use of statistics to demonstrate process understanding and to establish commercial manufacturing parameters
Acknowledgements

• Sharmista Chatterjee
• Ubrani Venkataram
• Alex Viehmann

• Questions, comments, concerns:
  – CDER-OPQ-Inquiries@fda.hhs.gov