

Using A PQRI Approach in Process Validation

Analysis of Powder Blends and Stratified
In-Process samples to demonstrate Unit
Dose Blend Uniformity

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Requirements

- FDA – 21 CFR 211.110 (a)(3)
 - Demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished dosage units.
- Health Canada Guidelines on Good Manufacturing Practices (GMP), Division 2, Part C of Regulation to the Food & Drugs Regulations require that:
 - All critical production processes must be validated

Powder Blend Uniformity

- Powder blends should be tested for uniformity based on samples that represent the final dosage amount (1-3X weight of the final dosage unit)
- Sounds simple enough,
 - obtain a sample thief capable of taking powder samples in the weigh range of your product
 - Take samples from predefined locations (minimum 10)
 - Test samples according assay methodology to meet blend uniformity specification
 - Pass – Blend is uniform
 - Fail – Blend is not uniform

Challenges

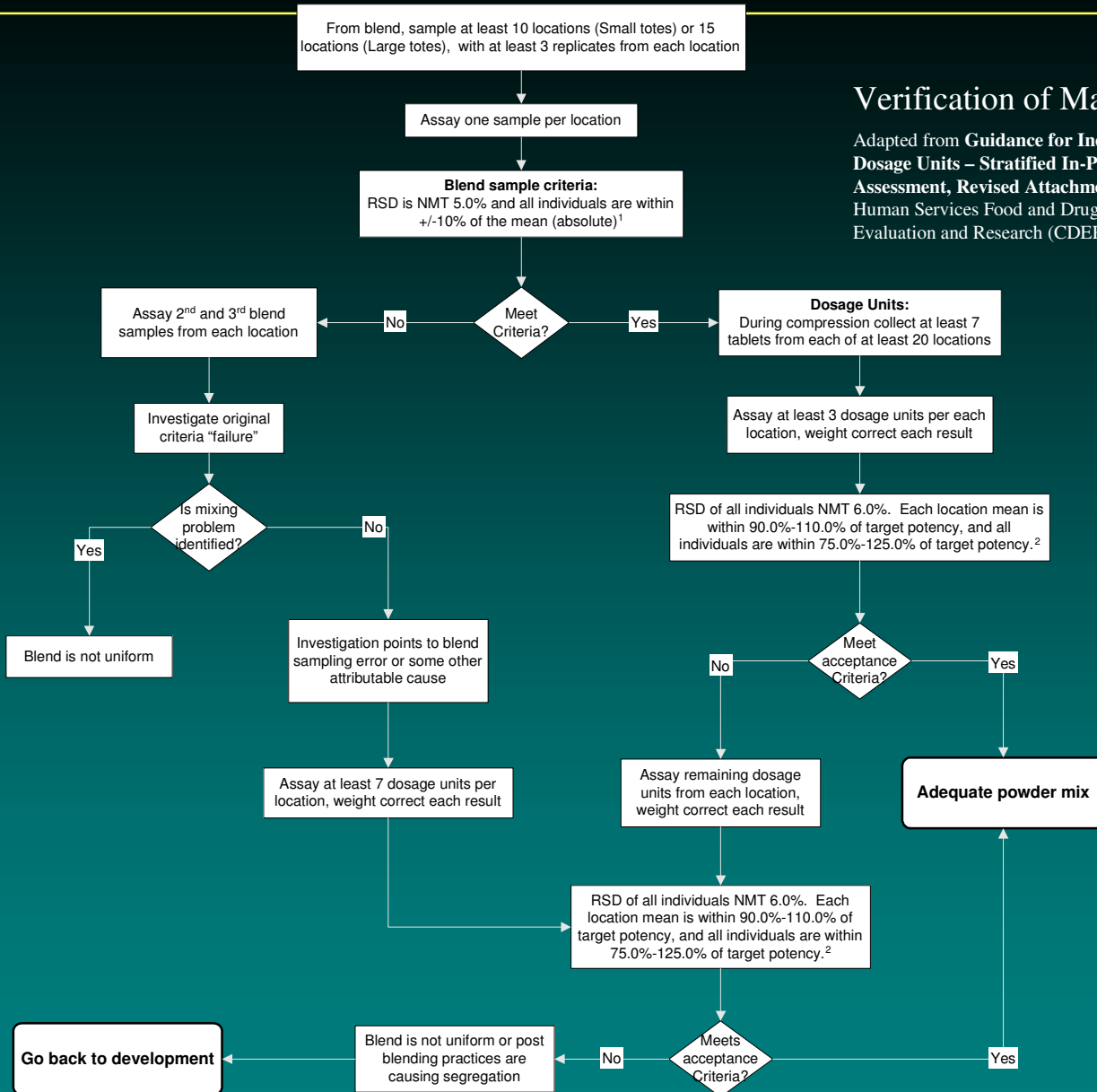
- Problem is not all blends are alike
 - Some blends may fail blend criteria but when compressed easily meet tablet content uniformity testing
 - Particle dynamics are complex and although blends may be adequately mixed and uniform in the blender or tote, sampling may cause localized segregation
 - Sampling is therefore a critical factor and may provide opportunity for variability or bias in your results
- To adequately characterize a blend you need a combination of both blend and finished tablet data

PQRI Approach

- PQRI is the “Product Quality Research Institute”, WWW.PQRI.ORG
 - 2000 PQRI formed a Blend Uniformity Working Group
 - 2002 submitted recommendation to FDA proposing an alternate strategy to assessing blend and dosage unit uniformity
 - 2003 FDA issued Draft Guidance for Industry “Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment”

Verification of Manufacturing Criteria

Adapted from **Guidance for Industry: Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment, Revised Attachments** --- U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), November 2003



¹ Examples of "mean \pm 10% (absolute)" are If mean strength = 103.0% then the interval is 103.0% \pm 10%, thus individual must fall within 93.0% to 113.0%

² When comparing individual dosage units to 75.0%-125.0% of target strength, use the as is results (not weight corrected)

Why Use the PQRI approach?

- Provides a reasonable, overall approach to evaluating blend and product uniformity
- Recognizes and allows for investigation of sampling error
- Relatively straight forward and easy to apply
- Allows for consistency

Blend Sampling

- Sampling is critical. It is important to minimize variability
 - Getting the right sample thief
 - Several models with multiple die sizes are commercially available
 - Training
 - Consistency!
 - Consistency in technique, operator
 - Consistency in weight (use appropriate weight range for the product)

Compression Sampling

- Stratified Sampling:
 - “Is the process of sampling dosage units at predefined intervals and collecting representative samples from specifically targeted locations in the compression/filling operation that have the greatest potential to yield extreme high and lows in test results”
 - Minimum 20 Locations
 - Focus on problem areas like initial start-up, end, or critical points in the process
 - May also need to identify end-of-batch with appropriate samples
 - Remaining locations can be equally distributed across the batch

Testing

- Consider having specific instructions in your assay method for blend sample handling (i.e. weight ranges, powder transfer technique)
- Triplicate samples
- Interpretation of results
 - Understanding variation and what it means to the overall uniformity of the blend (are there trends that may suggest a non-uniform blend or segregation?)
 - Weight corrected versus as is

Conclusions

- This approach is still in the draft form with FDA
- Health Canada has no published guidance specific to blend uniformity
- FDA draft identified some additional requirements around application to routine manufacture
“Standard Criteria (Readily Pass)” versus
“Marginal Criteria (Marginally Pass)”
- It is important that you characterize your product in development
 - Even though you may meet the PQRI criteria, you may decide to go back and modify the process
 - Marginally pass may mean more routine testing and/or potential for failure

Case Study

Unit Dose Blend Uniformity and
Stratified Sample Case Study

Case 1: Readily Pass

From blend, sample at least 10 locations (Small totes) or 15 locations (Large totes), with at least 3 replicates from each location

Assay one sample per location

Blend sample criteria:
RSD is NMT 5.0% and all individuals are within +/-10% of the mean (absolute)¹

Meet Criteria?

Yes

Blend Uniformity Results

-Average = 98.4%

-RSD = 2.5%

-Range = 94.3-102.1%

Blend Sample Criteria

- RSD NMT 5.0%?

- PQRI Acceptance Range 88.4-108.4%

Dosage Units:

During compression collect at least 7 tablets from each of at least 20 locations

Assay at least 3 dosage units per each location, weight correct each result

RSD of all individuals NMT 6.0%. Each location mean is within 90.0%-110.0% of target potency, and all individuals are within 75.0%-125.0% of target potency.²

Meet acceptance Criteria?

Yes

Adequate powder mix

Compression Results

-Location Averages = 95.2 to 101.8%

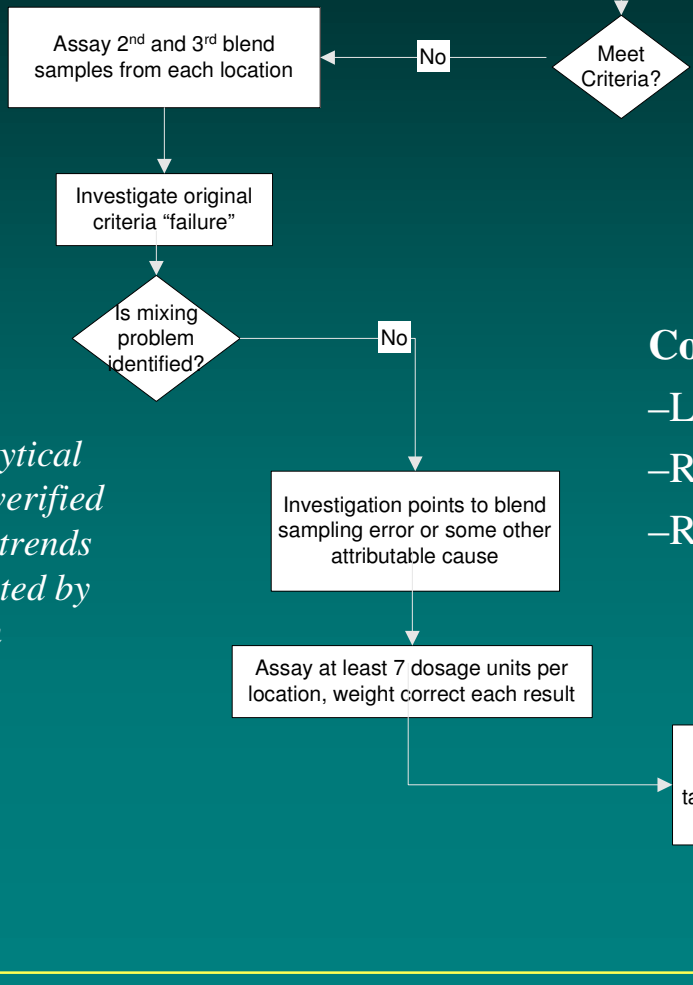
-RSD (n=60) = 3.4%

-Range (as is) = 92.5-105.5%

Case 2: Marginal Pass

2nd, 3rd

- Average = 103.9%, 102.8%
- RSD = 9.2%, 4.4%
- Range = 81.0-125.8%,
91.4-109.8%



All analytical results verified and No trends were noted by location

Blend Uniformity Results

- Average = 101.9%
- RSD = 5.9%
- Range = 93.7-119.2%

Blend Sample Criteria

- RSD NMT 5.0%?
- PQRI Acceptance Range 91.9-111.9%

Compression Results

- Location Averages = 95.1 to 102.1%
- RSD (n=140) = 3.2%
- Range (as is) = 90.1-106.7%

Adequate powder mix

Good to Go?

- Need to evaluate in relation to other batches
- Need to have solid investigation to support sampling error
- This may be considered “**Marginal**” based on FDA guidance
 - Could mean additional sampling/testing on routine production

References/Acknowledgements

- PQRI is the “Product Quality Research Institute”, WWW.PQRI.ORG
- “The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends”, Garth Boehm, Jon Clark, John Dietrick, Laura Foust, Thomas Garcia, Muralidhara Gavini, Loren Gelber, Jean-Marie Geoffroy, Pedro Jimenez, Gerald Mergen, Fernando Muzzio, Jerry Planchard, James Prescott, Jozef Timmermans, Neeru Takiar
- FDA – 21 CFR 211.110 (a)(3)
- Guidance for Industry (Draft), “Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, November 2003
- Health Canada Guidelines on Good Manufacturing Practices (GMP), Division 2, Part C of Regulation to the Food & Drugs Regulations