Process Validation Sampling for Non-Sterile Solid Dose Drug Products

Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

This document provides Process Validation Sampling guidelines for non-sterile solid dose drug product dosage forms.

The purpose of this document is to provide the general principles and approaches that should be considered for sampling non-sterile solid dosage forms. It is not intended to provide definitive validation sampling plans for use in every circumstance.

1. Validation Sampling of Granulations and Powder Blends:
There are many concerns regarding blend uniformity sampling, for example:

- Inappropriate sample thief technology;
- Powder segregation of samples may occur after sampling;
- Difficulty in proving that the blender sample plan will be representative of worst-case locations;
- Segregation of blend that can occur during discharge, storage, and transport prior to final processing.

Sampling concerns can be overcome if the sampling method is known and demonstrated to be capable. Refer to Appendix A for validation sampling guidelines for this category of product.

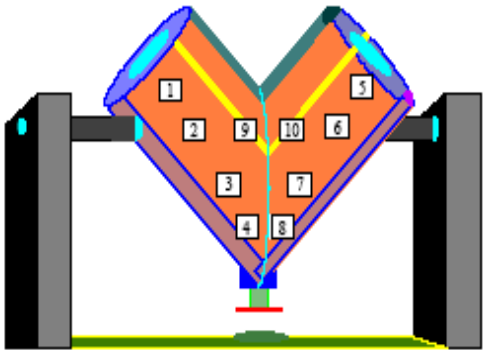
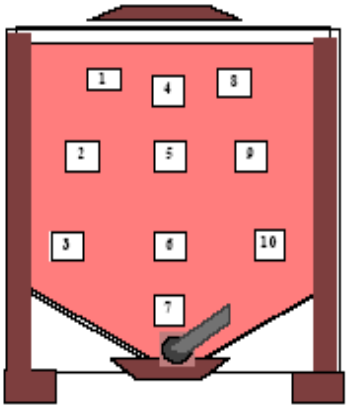
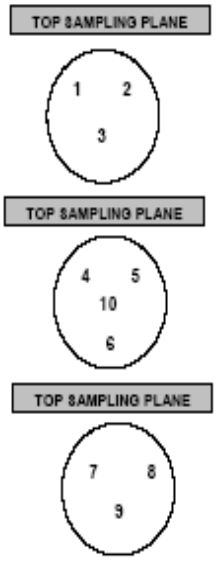
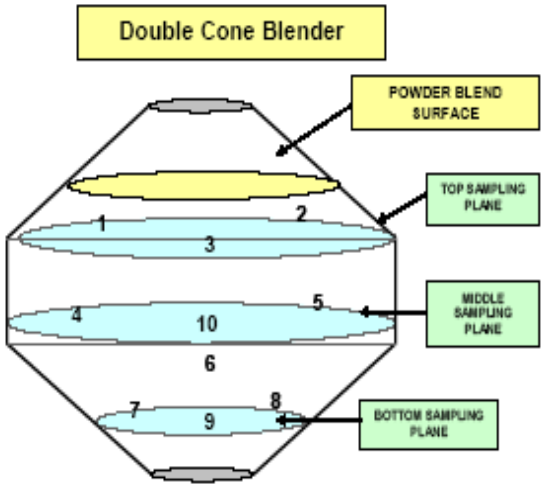
2. Validation Sampling of Solid Dosage Forms (Tablets, Capsules):
Solid dosage forms typically provide many opportunities for applying appropriate and scientifically sound sampling approaches.

Refer to Appendix B for validation sampling guidelines for this category of product.

The Product Quality Research Institute (PQRI) Blend Uniformity Group has developed an approach to demonstrating blend uniformity by combining blend testing with in-process dosage unit compendial testing. This approach postulates that the analysis of finished tablets/capsules can support or provide statistical evidence that a failing blend result was due to poor sampling or handling technique.

The PQRI approach was adopted in the FDA, Draft Document for Industry: Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment of October 2003. The sampling recommendations in this document are based on this document. Refer to Appendix C for validation sampling guidelines and flow chart.
Other sampling approaches and acceptance criteria maybe used if they are scientifically and statistically justified.

APPENDIX A: SAMPLING OF GRANULATIONS AND DRY POWDER BLENDS (Cont.):

Manufacturing Stage	Process Validation Sampling Guideline
Final Powder Blend	Example of Sampling points: PK-V-Blender  Bin Blender   Double Cone Blender 

APPENDIX C: STRATIFIED SAMPLING OF POWDER BLENDS AND FINAL SOLID DOSAGE UNITS (Cont.)

The following table shows the stratified sampling and test acceptance criteria to be conducted during validation as adopted by FDA (reference 1). The same information is represented on the next page in a decision flow chart.

Process Stage	Sampling	Test	Acceptance Criteria
Blending	Sample at least 10 locations, with 3 replicates per location	Assay 1 sample per location (second and third replicates will be used if needed)	RSD ≤ 5.0% and all individuals are within ±10% of mean (absolute)[a]

If…	Then…
Blend results comply with acceptance criteria	Continue to filling and compression sampling
Does not comply with acceptance criteria	Follow site SOP for OOS. Once completed, test 2nd and 3rd blend samples from each location and investigate original criteria "failure"
	Blend is not uniform and go back to development Mixing problem is identified
Mixing problem is not identified and investigation points to blend sampling error or some other assignable cause	Compare against acceptance criteria: RSD ≤ 5.0% and all individuals are within ±10% of mean (absolute)[a]
If criteria is not met	Blend is not uniform or post blending practices are causing segregation and process should go back to development

Filling or compression	Sample from 20 locations 7 units per location, with 3 replicates per location	Stage I: Assay 3 dosage units per each location, weight correct[b] each result	Stage I: RSD of all individuals (for each batch n = 60) ≤ 4.0%. Each location mean is within 90.0 – 110.0% of target strength All individuals results are within 75.0 – 125.0% of target strength[c]

[a] Examples of "mean +/- 10% (absolute)" are: If the mean strength = 95%, then the interval is 95% +/- 10%; thus, all individuals must fall within 85.0% to 105.0%. If the mean strength = 103.0%, then the interval is 103.0% +/- 10.0%; thus all individuals must fall within 93.0% to 113.0%.

[b] Weight correct is a mathematical correction to eliminate the effect of potentially variable tablet weight on measurement of mix adequacy. For example, a tablet with a strength of 19.4 mg and weight of 98 mg = 19.4 ÷ 98 = 0.198 mg/mg. Label claim is 20 mg per each 100 mg tablet, so the weight corrected result is 0.198 ÷ 0.20 * 100 = 99% of target blend assay.

Note: This normalization deviates from USP <905>, but is a more accurate measure of uniformity.

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

