

Title: Process Validation Sampling for Non-Sterile Solid Dose Drug Products					
Guidance Number: 038					
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

Process Validation Sampling for Non-Sterile Solid Dose Drug Products

Introduction

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

The purpose of this guidance 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.

Recommendations and Rationale for Recommendations

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.

APPENDIX A: SAMPLING OF GRANULATIONS AND DRY POWDER BLENDS

(Cont.):

Manufacturing Stage	Process Validation Sampling Guideline
Sizing	<p>Sizing: If the granulation is milled, dried, and then milled again; particle size verification is recommended to be performed during the last milling step. A representative sample from each of the following: start, middle, and end of the milling process should be collected. Each sample should be analyzed individually for particle size using the appropriate particle size analysis method, characterizing coarse, medium and fines fractions.</p> <p>Holding Time: Hold a representative portion of the final sized granulation for defined hold periods if applicable.</p>
Final Powder Blend	<p>Refer to Appendix C for an approach using stratified sampling of the blend and dosage units.</p> <p>A minimum of 10 locations distributed throughout the mixer/blender at three different levels (top, middle and bottom planes) typically should be sampled. Equipment geometry should be taken into consideration when establishing sampling locations within the mixing equipment. Sample location should include worst-case areas, such as known dead spots (justify rationale for location selection in protocol). For tumbling blenders (e.g. V-blenders, double cones, drum mixers), sample from at least two depths along the axis of the blender. For convective blenders (e.g. Ribbon blender), sample at least 20 locations to include the corners and discharge area.</p> <p>Sample size should not be greater than three times (3X) that of a dosage unit (one unit dose is preferred). However, the analytical test method should be consulted when writing the protocol to ensure that this is a sufficient amount of material for completion of testing. Sample quantities larger than 3X may be used if they can be scientifically justified (e.g. known sampling bias; 3X versus 5X sampling). Obtain a total of three samples from each location to ensure sufficient samples are available, should second level testing be required.</p> <p>If a common blend is used to manufacture multiple dosages (2.5 mg, 5.0 mg and 10.0 mg), the sample size to be used for the final blend sampling will be 3X the weight of the lowest dosage (e.g. 2.5 mg will be the worst case).</p> <p>If the blending equipment or load configuration prevents sampling directly from the blender, unit dose samples may be taken from at least ten points from the discharge stream or from the final holding container (drum or bin). These samples will be tested to demonstrate the homogeneity of the material.</p> <p>Acceptance criteria for blend uniformity should fulfil all applicable regulatory requirements for blend uniformity.</p> <p>Holding: Hold a representative portion of the final powder blend for defined hold periods if applicable.</p>

APPENDIX C: STRATIFIED SAMPLING OF POWDER BLENDS AND FINAL SOLID DOSAGE UNITS

Stratified Sampling (according to the FDA Draft Guidance for Industry: Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment) :

- Stratified sampling is the process of selecting units deliberately from various locations within a lot or batch or from various phases or periods of a process to obtain a sample.
- Blend sampling:
 - Blend uniformity will be demonstrated by assaying blend samples (unit dose by thief sampling) and dosage unit samples.
 - Stratified sampling of the blend and dosage units specifically targets locations either in the blender or throughout the compression/filling operation that have a higher risk of producing failing content uniformity results.
 - Identify at least 10 locations in the blender to pull blend samples
 - Locations must be carefully chosen to represent potential areas of poor blending. For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least 2 depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling, including the corners and discharge area (at least 20 locations are suggested to adequately validate convective blenders).
 - Take at least three replicate samples from each location.
- Compression/Tabletting Sampling:
 - Identify at least 20 locations throughout the compression or filling operation to obtain dosage units. There should be at least 7 samples taken from each of these locations for a total minimum of at least 140 samples.
 - Sampling points shall include specific activities that could potentially cause powder blend segregation such as start of dosage compression or filling, change of granulation bins, after each machine stop, after refreshment breaks, and at the end of the batch.
 - Sample collection should start after the compression or filling machine has been properly adjusted and product parameters are considered stable.
 - Sampling should include both sides of the compressing equipment.
- Samples should be collected for both blending and dosage stages.
- Testing should be performed on blending and Stage I samples and evaluated against acceptance criteria. Refer to the table on the following page.
- Out of specification results (as per protocol criteria) for blending and Stage I samples should be investigated by the analytical laboratory prior to testing Stage II samples (following site investigational procedure for Out of Specification (OOS) results).