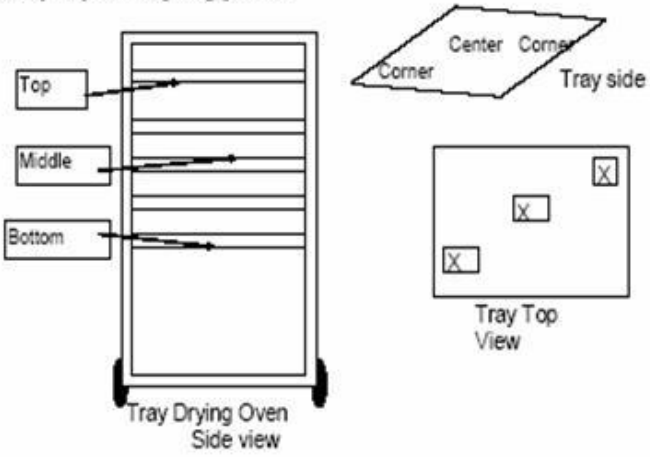
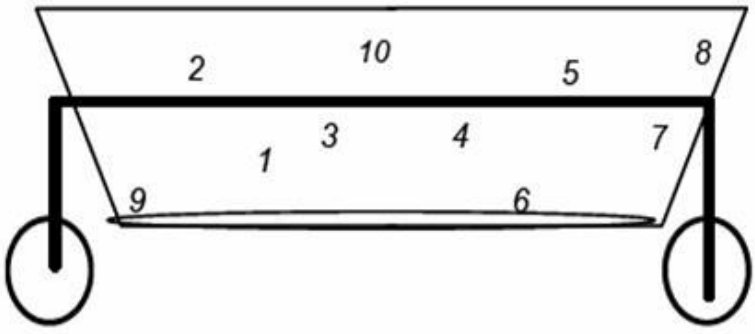
Guidance Number 38:

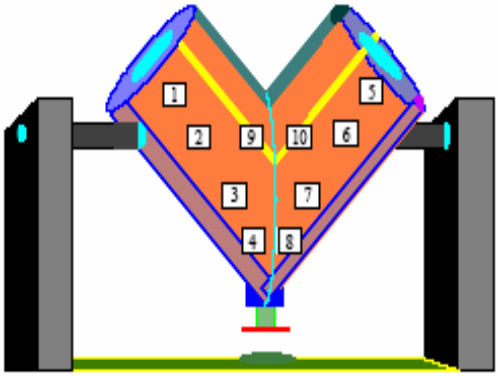
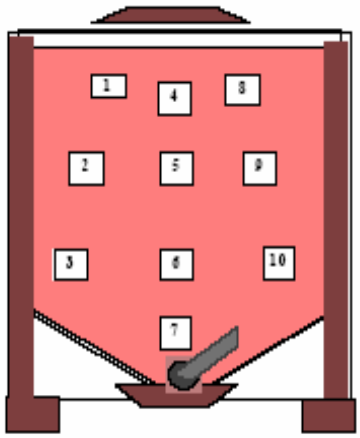
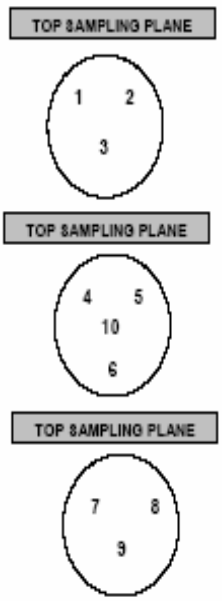
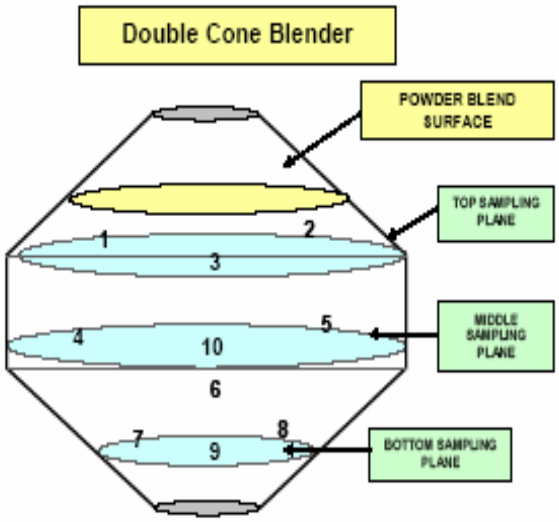
APPENDIX A: SAMPLING OF GRANULATIONS AND DRY POWDER BLENDS (Cont.):

Manufacturing Stage	Process Validation Sampling Guideline
Drying	**Drying:** Individual samples should be taken at, near or after the known drying endpoint and evaluated for moisture content. Equipment geometry should be taken into consideration when establishing sampling locations within the drying equipment. For fluid bed dryers, representative samples should be taken from each bowl of material and evaluated for moisture content. Samples can also be taken throughout the drying process using the equipment sampling port to justify the drying process. In this case, samples should be representative of the drying process (beginning, middle, endpoint, at process interruption, and after endpoint). For tray driers, samples are typically taken from the top, middle and bottom trays. Individual samples should not be combined to prepare a composite sample. E.g. Tray dryer sampling points:  E.g. Aeromatic tub - side view sampling points  **Holding Time:** Hold a representative portion of the dried granulation for defined hold periods if applicable.

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

Manufacturing Stage	Process Validation Sampling Guideline
Sizing	**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. **Holding Time:** Hold a representative portion of the final sized granulation for defined hold periods if applicable.
Final Powder Blend	Refer to Appendix C for an approach using stratified sampling of the blend and dosage units. 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. 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. 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). 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. Acceptance criteria for blend uniformity should fulfil all applicable regulatory requirements for blend uniformity. **Holding:** Hold a representative portion of the final powder blend for defined hold periods if applicable.

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   

APPENDIX B: SAMPLING OF SOLID ORAL DOSAGE FORMS

The following sampling plan example can be used as a guide for sampling solid oral dosage forms (tablets and capsules) and should be evaluated on a case-by-case basis.

Manufacturing Stage	Process Validation Sampling Guideline
Tabletting/ Capsule Filling	A minimum of 10 points should be sampled over the duration of the tabletting / encapsulation process for a batch under evaluation, including samples from the start, middle and end of the batch. Tablets / capsules should be collected at the final point in this step of the process (i.e. post metal detector). If blend uniformity issues have been identified, then refer to Attachment C for an example of a stratified plan in which 20 sampling points are recommended. Samples should be taken throughout the compressing /capsule filling run per machine side and be evaluated for: - assay/content uniformity (e.g. 30 dosage units/side) - weight - dissolution (e.g. 18 dosage units total, 6 each from beginning, middle and end as outlined by the USP) - dissolution profile (if applicable) (e.g. 6 tablets from each side). A composite sample from samples taken throughout the compressing/capsule filling run should be evaluated for conformance with internal control specifications (if final product is capsule or uncoated tablet). These composite samples may also be evaluated for appearance using, for example, ANSI/ASQ Z1.4-2003, Sampling Procedures and Tables for Inspection by Attributes. Sample size should be determined using this standard. **Holding Time**: Hold representative portion of cores or final tablet/capsule bulk for defined periods
Coating / Printing	Sufficient sample should be taken from each coating pan and be evaluated for: - assay and moisture content - dissolution - dissolution profile (if applicable) A composite sample from each coating pan load should be evaluated for content uniformity and all tests included in the internal control specifications (e.g. tablet weight, dissolution). Perform a visual inspection on a composite sample of both unprinted and printed tablets.

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).

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 $\leq$ 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 $\leq$ 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) $\leq$ 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).

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

Filling or compression

If…	Then…
Stage I and blending results comply with acceptance criteria	Process produces a uniform Blend and Product
Blending results comply with acceptance criteria but compression/filling Stage I does not comply with acceptance criteria	Follow Stage II testing and criteria

Filling or compression	Stage II: Assay remaining 4 dosage units per each location (7 per location altogether), weight correct[b] each result	Stage II: RSD of all individuals (for each batch n = 140) $\leq$ 6.0%. 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]
Stage II criteria is not met	Blend is not uniform or post blending practices are causing segregation and process should go back to development	

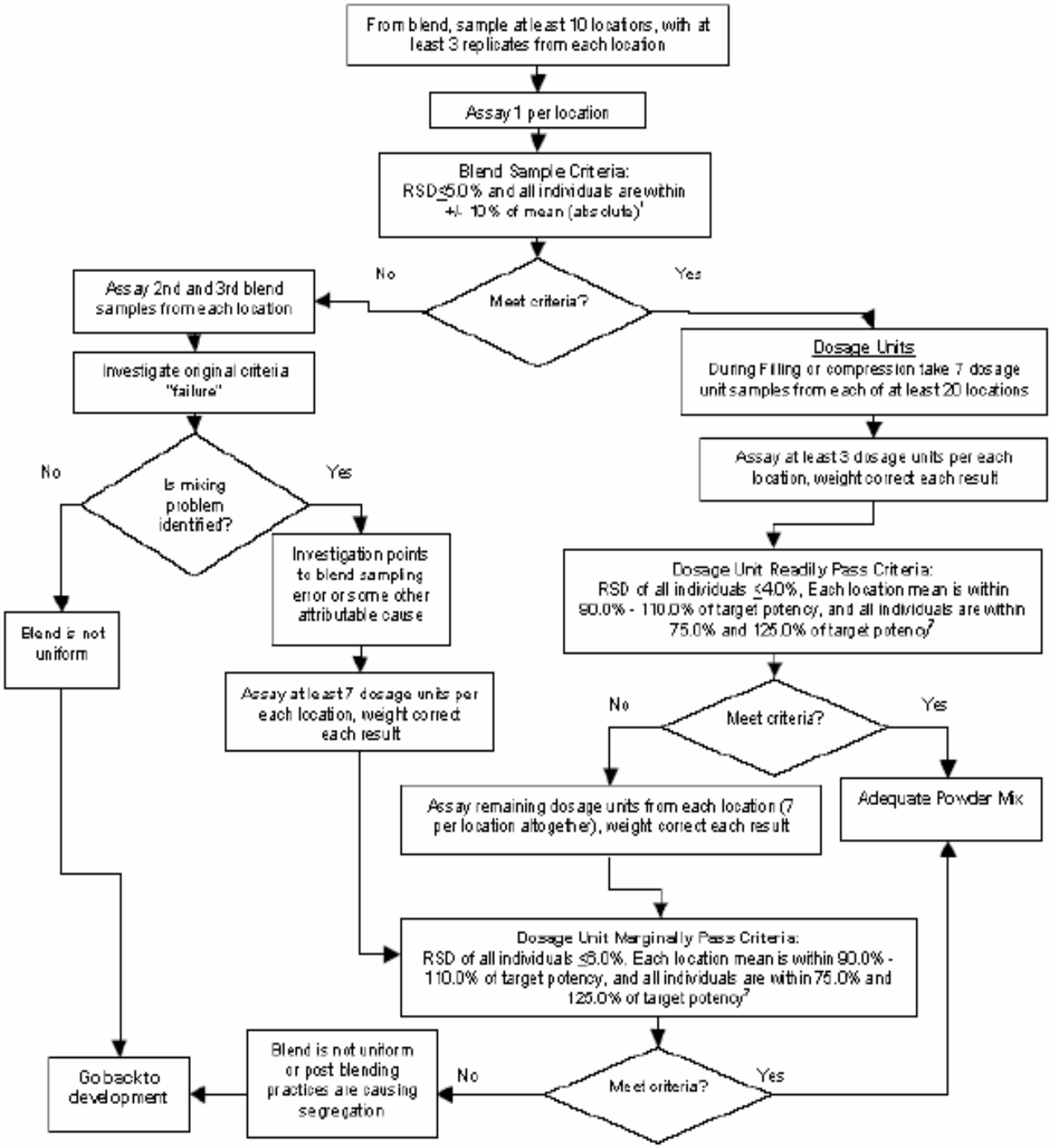
[b] Weight correct is a mathematical correction to eliminate the effect of potentially variable tablet weight on measurement of mix adequacy. For example, a tablet with a strength of 19.4 mg and weight of 98 mg = 19.4 ÷ 98 = 0.198 mg/mg. Label claim is 20 mg per each 100 mg tablet, so the weight corrected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

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

ATTACHMENT 1: VERIFICATION OF MANUFACTURING CRITERIA



[1] 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%.

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