Sampling plans must be developed to consider the specific attributes being measured and the risks associated with accepting a defective lot. Sampling plans and methods must be predetermined and documented in a protocol. Colleagues involved must be trained.

The sampling procedures documented in the protocol should provide sample locations, sample size, sample frequency and should also include the tests or assessments required.

Samples must be representative of the population and the sampling plan must be designed to determine any segregation during blending, transport, or handling and any variability or other factors that might impact production consistency.

The need to show homogeneity of intermediates should be considered on a case-by-case basis depending on how the intermediate is used in subsequent processing. In general, studying the homogeneity of an intermediate is of less importance than that of a final product, especially if the intermediate will be further processed in the next or final step of the process. If homogeneity of the intermediate is critical to the quality of the final product prepared from it, demonstration of intermediate blend homogeneity should be considered.

Sample size, frequency and location for tests other than homogeneity will be determined on a test by test basis and documented in a validation protocol. **Section 5.2** to **5.10** is applicable to homogeneity sampling and testing only.

5.2 **Blend Sample Size**

Blend sample size should be as specified in **LAB-125** *Sampling of Raw Materials, In-process and Bulk Finished Product.*

5.3 **Sampling Locations**

5.3.1 **Blend Uniformity Sampling**

For tumble blending, at least 10 locations in the blender should be sampled and must be chosen to represent potential areas of poor blending. At minimum samples should be selected from at least 2 depths along the axis of the blender. For ribbon blending, at least 20 locations in the blender should be sampled and must be chosen to adequately address potential dead spots such as corners and discharge areas. Equipment geometry should be taken into consideration when establishing sampling locations.

Blend uniformity samples should be sampled directly from the blender immediately prior to discharge. If it is not practical to take samples from the blender, samples may be taken from the discharge stream or drums/tote bins. At least three replicate samples will be taken from each location with one samples tested per location.

Blend uniformity acceptance criteria: RSD =5.0% and all individuals are within the mean ± 10% (absolute).

5.3.2 **Finished Product (Dosage Unit) Sampling**

The number of samples taken for each validation study should be based on risk. For example, the risk to a patient from a new formulation may be significantly higher than

following guideline should be considered at minimum for filling / packaging sampling:

- Beginning of Filling (ideally first 10 packages kept as product for sale): 10 samples
- Middle (taken from throughout the middle of the filling operation): 10 samples
- End (ideally the very last containers packaged that would be kept as product for sale): 10 samples

In addition if there are critical occurrences during the packaging run which may affect the product, then sampling at start-up immediately following such an event should be considered. The rationale behind collection and/or testing of these samples should be outlined in the protocol.

5.7 **Raw Material Change**

A change in supplier or manufacturer of a raw material is assessed as per SOP **VAL-105** *Raw Material Evaluation Process*. Where a change is made to an active or excipient in a formulation and where revalidation is required, sampling requirements will be based on risk and documented in the Raw Material Evaluation Report.

For those products where routine blend testing is not performed, an assessment of the impact on blend uniformity and the requirements of the blend specification must be performed. Additional monitoring and testing during or post validation batches may be required. This will be documented either in the validation protocol or Raw Material Evaluation.

5.8 **Process Change (Including Equipment)**

Each process change should be address individually and the validation requirements documented in the protocol as per SOP **VAL-115** *Process Validation for Liquids and Solid Dose Manufacture.* Sampling and testing should be based on risk. If the number of samples taken is different to the number specified in this SOP, a documented justification must be included in the protocol.

For those products where routine blend testing is not performed, an assessment of the impact on blend uniformity and the requirements of the blend specification should be performed. Additional monitoring and testing during or post validation batches may be required. This will be documented either in the validation protocol or a risk assessment. Once validated it is not considered necessary to continue blend testing.

5.9 **QC Reductive NIR Sampling and Testing**

Content uniformity testing of finished product validation samples may be performed by a combination of NIR and specification testing (QC Reductive Testing). NIR testing may be used to qualitatively determine the content uniformity spread for the batch under validation. Specification testing of the extremes of the spread will allow full characterization of the content uniformity.

Batch release testing will be performed as per specification test requirements and must be included in the validation report.

A validation batch using QC reductive testing must meet all QC reductive test requirements for the validation samples and specification requirements for the release for sale samples.

