- Review results for each batch in the study
- Compile results in a Process Validation Report
- Audit and verify data
- Issue Validation Report and obtain approval

5.1.2 **Prerequisites for Process Validation**

Prerequisites for Process Validation include, and are not limited to, the following:

- Approved master formula, master manufacturing instructions, and applicable SOPs;
- Identification of Critical Process Parameters;
- Equipment Qualification (including laboratory equipment) - facilities, utilities, systems, (including Computerized Systems), and equipment (including filling equipment used in the packaging operation of liquid and semi-solid processes) to be used shall have been qualified prior to validation of the manufacturing process;
- Supporting processes that may affect process validation (e.g., equipment cleaning), shall be qualified;
- Calibration of critical instruments;
- Approved specifications for finished product, in-process testing, raw materials, and components;
- Validated test methods shall be used;
- Personnel taking part in the validation work shall have been trained and qualified before carrying out such work, with training records documented.

5.2 **Process Validation Protocol**

The validation protocol is a written plan stating exactly how the validation study will be conducted. In general, the protocol explains what will be done to validate the specific process, how it will be executed, who will execute it, and what the acceptance criteria are. Any deficiencies in the prerequisites detailed above must be resolved prior to proceeding with protocol execution or a justification documented in the protocol which will be approved by at minimum the Validation Manager, Quality Assurance Manager and the Process Owner or their delegates, by approving the protocol for execution.

5.2.1 **Basic Document Format**

Each protocol and report should contain on its cover page:

- Protocol title, number, and version number
- Product name, strength and item number
- Signature and date of the protocol author, reviewer(s) and approvers

5.2.2 **Objective**

The objective of the protocol should be concisely stated. In general, the objective of any study should be to assure that the process/product consistently meets all pre-determined acceptance criteria and specifications and will provide a high degree of assurance that the process will produce a product that consistently meets site quality control specifications for the product. The objective should also include a reference to the change control.

5.2.3 **Scope**

5.3.7 **Calibration**
All critical instruments that are used to control, measure or monitor direct or indirect process parameters should be within calibration throughout the validation study. List all critical instruments and calibration status. Attach or reference the calibration details and verify calibration status during the validation study.

5.3.8 **Standard Operating Procedures and Training**
Verify that the required Standard Operating Procedures are current, approved and that the appropriate persons have been trained in those procedures.

5.3.9 **Environmental Monitoring**
Environmental monitoring must be included during validation for those processes that require manufacturing to be conducted in a controlled environment. Monitoring may include temperature, relative humidity, and microbiological environmental sampling. Monitoring may be performed by exception.

5.4 **General Sampling, Monitoring and Assessment Procedure**
Verify each unit operation by monitoring operating conditions, sampling and testing, or both. If the initiation of validation is for a modification, then those stages not affected by the processing step to be modified may be eliminated from the sampling and monitoring plan, assuming no benefit is anticipated from collecting this information. The rationale behind not including this testing must be stated in the protocol. Evaluation of processing stages that follow the modified step must be considered individually for impact and included in the study accordingly.

Critical Processing Parameters should be identified, and where possible, monitored, sampled or tested. These points may include intermediates and finished products. The protocol must include the type, amount and number of samples to be collected, where samples are to be taken, and any special sampling or handling requirements.

If necessary, a detailed description of the sampling procedure must be included. Sample amounts must be based on the amount required by the test method, sampling device, and dosage size as per Site sampling procedure. The protocol should allow for recording of sample number, sample time and date and sampled by information.

This section should also define the critical areas to be monitored based on the critical process steps. Critical processing points will be identified on a case-by-case basis and included in the validation protocol.

General sampling techniques for different product types are detailed below.

5.4.1 **Homogeneity**
Sampling plans must be developed to demonstrate homogeneity throughout the batch. The bulk/blend must be representatively sampled based on product type, mixing container geometry and process (e.g., mixing mechanism) on completion of the processing step. Additional sampling on completion of discrete critical steps may also be performed. Sampling must not impact on the quality of the final bulk mixture. Representative samples must be drawn after critical process steps. Sampling plans must take into account start up requirements, process control frequency, line stops or

Documentation of the reason for batch elimination, replacement intentions, and a reference to the formal investigation report must be generated.

If a validation batch fails to meet the acceptance criteria, and results in a change to the process steps and/or acceptance criteria, the original validation protocol may be amended and re-approved as the next version.

Three consecutive, successful batches must then be manufactured to demonstrate that the modified process is under control, and reproducible. All failed batches must be referenced in the validation report.

5.6 **Process Validation Report**

The final Validation report references the relevant protocol(s) and summarises the results of the validation study. Using the protocol as a guide, this document includes a review of the results of each phase of the study, and provides summaries and illustrations of the data. The report should provide sufficient information to detail the validation study without requirement to review the validation protocol. The report is reviewed and approved by the same persons or designees that reviewed and approved the protocol.

A final report should be issued following completion of the validation study. Interim reports are required for concurrent validation batches. Interim reports should contain where relevant the same details as a final report.

5.6.1 **Document Format**

Each report should contain on its cover page:

- Report title, number, and revision number
- Product name and strength
- Signature and date of the protocol/report author, reviewer and approvers.

5.6.2 **Objective**

The objective of the report should be concisely stated. In general, the objective of the report should be to assure that the process/product consistently meets all pre-determined acceptance criteria and specifications and will provide a high degree of assurance that the process will produce a product that consistently meets site quality control specifications for the product.

5.6.3 **Scope**

As in the protocol, the report should clearly define the product to be validated. The protocol number and version and the change control number should be referenced. If the protocol version is not version 1, rationale for the protocol version must be provided. Any supplemental documentation should also be referenced. An explanation for supplemental documentation should be provided.

5.6.4 **Responsibilities**

The responsibilities for review and approval of the report should be detailed.

5.6.5 **Validation Strategy**

An overview of the validation strategy as detailed in the validation protocol should be detailed in the report. Any departures from the planned strategy should be detailed in this section.

