Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

1 Purpose

The purpose of this document is to provide guidance on the validation of processes for the manufacture of bulk drug i.e. those synthetic stages from introduction of the defined API Starting Materials into the process up to and including the physical processing of the API (Active Pharmaceutical Ingredient).

Validation should extend to those operations determined to be critical to the quality and purity of the API. The validation of stages prior to the API Starting Materials is not mandatory. A risk assessment may deem it necessary.

2 Scope and Applicability

All functions, departments and manufacturing sites or their contractors. The manufacture of intermediates post API starting materials up to and including final API, for onward sale external to the site or for use in site formulated products.

3 Definitions

3.1 Process Validation

Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

3.2 Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Note: for process validation, the protocol would identify the number of validation batches.

3.3 API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API

The validation of a process for a product that has been marketed based upon accumulated manufacturing, testing and control batch data. It may be used as the basis to support (but not in lieu of) prospective/concurrent validation activities.

5.2.4 Prior to Commercial Process

Process validation activities during product development are the responsibility of the development function. Development reports provide a repository of product knowledge that the processing and testing are understood. In addition they help in setting process parameters by providing information on worst case testing carried out on small-scale laboratory batches.

5.2.5 Commercial Process

It is the responsibility of the manufacturing site to ensure that all manufacturing processes used for commercial materials are validated. Prospective validation, follows a pre-prepared validation protocol that derives any critical parameters /activities and acceptance criteria from the product development/scale up/optimization experiences for new products, and/or from historical manufacturing information on existing processes. Validation should be undertaken under the fixed process conditions to be used for routine manufacture using appropriately trained individuals.

5.3 New and Modified Products and Processes

For new or modified product or processes, it is now frequent practice to derive parameter ranges from Factorial Experimental Design (FED) work in the laboratory, then to establish the process on the plant using Established Parameter Ranges (EPR).

There is invariably a period of experimental manufacture on plant, during which processing conditions may be adjusted until optimization of the process is achieved. This experimental work should be carried out in accordance with a program, which should specify the objectives, methods and criteria for completion of the work.

When all experimental work has been successfully completed and the product or process can be considered established, it still requires validation to provide assurance that it satisfies its intended purpose, that is, to consistently yield a product of the required quality. Validation should be carried out after completion of the experimental or establishment phase and should normally cover the manufacture of three consecutive batches nominated in advance.

Minor changes are allowed between establishment and validation but critical process parameters must remain unchanged.

An example of processing steps normally covered in a validation program are shown in the table in appendix 1, together with examples of objectives, sampling & testing and acceptance criteria for each step. This information should be used only as a guideline, however, and appropriate programs should be produced to

Process Step	Objective	Sampling & Testing	Criteria for Acceptance
	To Demonstrate:		
Centrifuge and Pressure Filter (wet paste discharge)	Consistent operation of centrifuge. Batch Consistency/conversion/washing	Sample: B,M,E Test: LOD (Loss on Drying), Strength, Related Substance(s).	LOD in - process limit Strength, related substance(s) to be in spec.
Dryer (batch e.g. agitated vacuum or pressure filter)	Uniformity of drying conditions & batch homogeneity. Effectiveness of normal Intermediate sampling.	Sample: B,M,E and composite Test: B,M,E for LOD, solvents, strength, related substances. Composite: full spec test.	LOD in process limit. Strength, related substance solvents in spec and eg +/- x % of mean. See Note 2 below.

Process Step	Objective	Sampling & Testing	Criteria for Acceptance
Mill API	Effectiveness of milling. Effectiveness of the complete purification process & batch homogeneity. Effectiveness of normal end product sampling.	Sample: B,M,E and composite. Test: B,M,E for strength, related substances, solvent(s) water, particle size and/or SSA. Composite: full spec test.	All results in spec. and see Note 2 below.

